Report on the Deliberation Results

August 16, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Tasfygo Tablets 35 mg
Non-proprietary Name	Tasurgratinib Succinate (JAN*)
Applicant	Eisai Co., Ltd.
Date of Application	December 18, 2023

Results of Deliberation

At its meeting held on August 2, 2024, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

** Japanese Accepted Name (modified INN)*

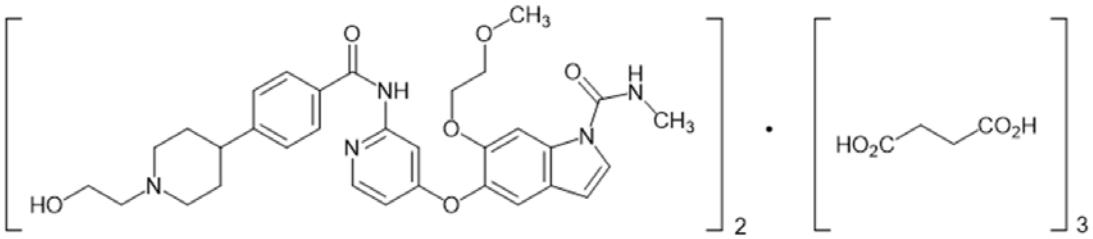
Review Report

July 19, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Tasfygo Tablets 35 mg
Non-proprietary Name	Tasurgratinib Succinate
Applicant	Eisai Co., Ltd.
Date of Application	December 18, 2023
Dosage Form/Strength	Tablet: Each tablet contains 45.5 mg of tasurgratinib succinate (equivalent to 35 mg of tasurgratinib).
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $(C_{32}H_{37}N_5O_6)_2 \cdot (C_4H_6O_4)_3$
Molecular weight: 1529.60
Chemical name: 5-[2-({4-[1-(2-Hydroxyethyl)piperidin-4-yl]benzoyl}amino)pyridin-4-yl]oxy-6-(2-methoxyethoxy)-*N*-methyl-1*H*-indole-1-carboxamide sesquisuccinate

Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 503 of 2021 [*R3 yaku*]; PSEHB/PED Notification No. 0219-1 dated February 19, 2021, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of unresectable biliary tract cancer with *fibroblast growth factor receptor 2 (FGFR2)* gene fusion that has progressed after cancer chemotherapy, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. Hyperphosphatemia, retinal detachment, eye disorders (except for retinal detachment), nail disorders, and palmar-plantar erythrodysesthesia syndrome should be further investigated in post-marketing surveillance.

Indication

Unresectable biliary tract cancer with *fibroblast growth factor receptor 2 (FGFR2)* gene fusion that has progressed after cancer chemotherapy

Dosage and Administration

The usual adult dosage is 140 mg of tasurgratinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

June 5, 2024

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Tasfygo Tablets 35 mg
Non-proprietary Name	Tasurgratinib Succinate
Applicant	Eisai Co., Ltd.
Date of Application	December 18, 2023
Dosage Form/Strength	Tablet: Each tablet contains 45.5 mg of tasurgratinib succinate (equivalent to 35 mg of tasurgratinib).
Proposed Indication	Unresectable biliary tract cancer with *fibroblast growth factor receptor 2 (FGFR2)* gene fusion in patients who have received prior cancer chemotherapy
Proposed Dosage and Administration	The usual adult dosage is 140 mg of tasurgratinib administered orally once daily. The dose may be reduced according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

The binding of a fibroblast growth factor (FGF) ligand to fibroblast growth factor receptor 2 (FGFR2), a receptor tyrosine kinase, leads to dimerization and activation of EGFR2, resulting in activation of the downstream signaling pathways such as mitogen-activated protein kinase (MAPK) pathway, which would be involved in cellular proliferation, survival, and other activities (*Cancer Discov*. 2013;3:264-279, *Mol Cancer Res*. 2010;8:1439-1452, etc.). In tumor cells harboring *FGFR2* gene fusions with other genes, FGFR2 is considered to form dimers in a ligand-independent manner, thus constitutively activating the downstream signaling pathways, stimulating cellular proliferation (*Nat Rev Cancer*. 2017;17:318-332, *Int J Mol Sci*. 2020;21:6856).

Tasurgratinib Succinate (hereinafter referred to as "tasurgratinib") is an FGFR-inhibiting low-molecular-weight compound that was discovered by the applicant and is considered to inhibit FGFR2 phosphorylation and phosphorylation of the downstream signaling molecules, thus preventing the proliferation of tumor cells harboring *FGFR2* gene fusions.

1.2 Development history, etc.

The applicant initiated a Japanese phase I study (Study 101) in patients with advanced solid cancers in October 2014. Subsequently, starting in January 2020, the applicant conducted a global phase II study (Study 201) in patients with unresectable cholangiocarcinoma (intrahepatic or hilar cholangiocarcinoma) with *FGFR2* gene fusion who had received prior chemotherapy.

As of April 2024, tasurgratinib has not been approved in any country or region.

In Japan, patient enrollment in the global phase II study (Study 201) started in January 2020.

The applicant has filed the application for marketing approval for tasurgratinib based mainly on the results of Study 201.

Tasurgratinib was designated as an orphan drug in February 2021 with the intended indication of "unresectable biliary tract cancer harboring *FGFR2* gene fusions" (Orphan Drug Designation No. 503 of 2021 [*R3 yaku*]).

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder. The determined general properties include description, solubility, acid dissociation constant, partition coefficient, pH, melting point, thermal analysis, hygroscopicity, and crystalline polymorphism.

The chemical structure of the drug substance was elucidated by elemental analysis, ultraviolet-visible spectroscopy (UV-VIS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR) (^{1}H-NMR and ^{13}C-NMR), mass spectrometry (MS), and single-crystal X-ray diffraction.

2.1.2 Manufacturing process

The drug substance is synthesized using the following starting materials: [redacted], [redacted], [redacted], [redacted], and [redacted].

The quality control strategy has been developed based on the following investigations (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) based on quality risk assessment and the design-of-experiment method, and investigation of the acceptable ranges of manufacturing process parameters

Table 1. Summary of control strategy for the drug substance

CQA	Control methods
Identification	Specifications
Content (active ingredient and succinic acid)	[redacted], specifications
Related substances	[redacted], specifications
Residual solvents and residual amines	[redacted], specifications
Particle size	[redacted], specifications
Microbial limit	Specifications

[redacted] have been defined as critical steps. [redacted], [redacted], [redacted], and [redacted] are controlled as critical intermediates.

2.1.3 Control of the drug substance

The proposed specifications for the drug substance consist of content, description, identification (IR), purity (related substances [high performance liquid chromatography (HPLC)] and residual solvents [gas chromatography (GC)]), water content, particle size, microbial limit, and assay (drug substance [HPLC] and succinic acid [HPLC]).

2.1.4 Stability of the drug substance

Table 2 shows the main stability studies performed on the drug substance. The results demonstrated the stability of the drug substance. Photostability testing showed that the drug substance was photolabile.

[redacted]

Table 2. Stability studies of the drug substance

Study	Batch scale	Temperature	Humidity	Storage condition	Storage period
Long-term	3 commercial-scale batches	5°C	-	Polyethylene bag + aluminum-laminated bag	24 months
Accelerated		25°C	60% RH		6 months

In view of the above, a retest period of [redacted] months was proposed for the drug substance placed in a polyethylene bag, which was then stored in an aluminum-laminated bag at 5°C, in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1E guideline. The long-term testing will be continued for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is an immediate-release film-coated tablet. Each tablet contains 45.5 mg of Tasurgratinib Succinate (equivalent to 35.0 mg of tasurgratinib). Excipients contained in the drug product are lactose monohydrate, low substituted hydroxypropylcellulose, hypromellose, magnesium stearate, and Opadry [redacted].

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of the following steps: [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], tableting, coating, [redacted]/filling/packaging/labeling, storage, and testing. With use of continuous manufacturing technology, the steps from [redacted] to [redacted] are operated in an integrated system. The steps [redacted], [redacted], and [redacted] are performed continuously by [redacted].

The quality control strategy has been developed based on the following investigations (Table 3):

- Identification of CQAs
- Investigation of CPPs based on quality risk assessment and investigation of the acceptable ranges of manufacturing process parameters
- Application of real time release testing (RTRT) to [redacted]

Table 3. Summary of control strategy for the drug product

CQA	Control methods
Identification	Specifications
Strength	[redacted], specifications
Related substances	[redacted], specifications
Strength uniformity	[redacted], specifications
Dissolution	[redacted], specifications

[redacted] has been defined as a critical step. In-process control parameters and control values have been established for the following steps: [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted].

2.2.3 Control of the drug product

The proposed specifications for the drug product consist of strength, description, identification (ultraviolet spectroscopy and HPLC), purity (related substances [HPLC]), uniformity of dosage units (content uniformity test [UV-VIS]), dissolution (UV-VIS), microbial limit, and assay (HPLC).

For [redacted], RTRT ([redacted] for [redacted]) performed as an in-process test has been established as the release testing for the drug product. When RTRT cannot be applied to the release testing, specification tests are performed in accordance with the predefined conformity standards and operating procedures to make a release decision.

2.2.4 Stability of the drug product

Table 4 shows the main stability studies performed on the drug product. The results demonstrated the stability of the drug product. Photostability testing showed that the drug product was photostable.

Table 4. Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 commercial-scale batches	25°C	60% RH	Blister pack (polyvinyl chloride/aluminum)	24 months
		30°C	75% RH		
Accelerated		40°C	75% RH		6 months

In view of the above, a shelf life of 36 months was proposed for the drug product packed in a blister pack (polyvinyl chloride/aluminum) at room temperature in accordance with the ICH Q1E guideline. The long-term testing will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA has concluded that the quality of the drug substance and the drug product is controlled adequately.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

In this section, the doses and concentrations of tasurgratinib and its metabolites are expressed as the free base.

3.1 Primary pharmacodynamics

3.1.1 Binding to FGFR (CTD 4.2.1.1.4)

The binding site of tasurgratinib on human FGFR1 was investigated by X-ray crystallography using cocrystals of FGFR1 (recombinant protein) and tasurgratinib. The results suggested that tasurgratinib mainly binds to the adenosine triphosphate (ATP) binding site and allosteric site of FGFR1.

3.1.2 Inhibitory effect on the kinase activity of FGFR and related substances. (CTD 4.2.1.1.1, 4.2.1.1.2, 4.2.1.1.3, and 4.2.1.1.7)

The inhibitory effect of tasurgratinib on the kinase activity of human FGFR1 to FGFR4 and vascular endothelial growth factor receptor (VEGFR) 2 (recombinant protein) was investigated by mobility shift assay. Table 5 shows the 50% inhibitory concentration (IC_{50}) values of tasurgratinib against FGFR1 to FGFR4 and VEGFR2.

Table 5. Inhibitory effect of tasurgratinib on FGFR1 to FGFR4 and VEGFR2

Kinase	IC_{50} (nmol/L)
FGFR1	0.891 ± 0.0606
FGFR2	0.557 ± 0.0257
FGFR3	1.76 ± 0.0309
FGFR4	124 ± 7.54
VEGFR2	18.2 ± 0.546

Mean ± standard deviation, n = 3.

The inhibitory effect of tasurgratinib on the kinase activity of 141 human kinases (recombinant proteins) was investigated by mobility shift assay. Table 6 shows the kinases inhibited by tasurgratinib with an IC_{50} of ≤20 nmol/L.

Table 6. Inhibitory effect of tasurgratinib on FGFR and other kinases

Kinase	IC_{50} (nmol/L)	Kinase	IC_{50} (nmol/L)
FGFR1	1.12	RET	4.13
FGFR2	0.412	RET^{G691S} *3	4.72
FGFR3	1.42	RET^{M918T} *4	15.5
$FGFR3^{K650E}$ *1	5.51	RET^{S891A} *5	1.85
$FGFR3^{K650M}$ *2	18.4	RET^{Y791F} *6	5.37
DDR1	7.27	VEGFR1	7.13
DDR2	4.84	VEGFR2	19.8

n = 1. *1, substitution of lysine at position 650 by glutamic acid; *2, substitution of lysine at position 650 by methionine; *3, substitution of glycine at position 691 by serine; *4, substitution of methionine at position 918 by threonine; *5, substitution of serine at position 891 by alanine; *6, substitution of tyrosine at position 791 by phenylalanine.

The inhibitory effects of the tasurgratinib metabolites M2 and (*R*)-M9 [see Sections 4.3.1, 4.5.1, and 6.2.2.1] on the kinase activity of human FGFR1 to FGFR4 and VEGFR2 (recombinant proteins) were investigated by mobility shift assay. Table 7 shows the IC_{50} values of tasurgratinib against various FGFR kinases.

Table 7. Inhibitory effect of tasurgratinib metabolites on human FGFR1 to FGFR4 and VEGFR2

Tasurgratinib metabolite	Kinase	IC_{50} (nmol/L)
M2	FGFR1	0.946 ± 0.136
	FGFR2	0.369 ± 0.0327
	FGFR3	1.40 ± 0.104
	FGFR4	92.5 ± 15.9
	VEGFR2	16.3 ± 1.84
(*R*)-M9	FGFR1	2.76 ± 0.322
	FGFR2	0.950 ± 0.0534
	FGFR3	3.10 ± 0.0392
	FGFR4	136 ± 2.03
	VEGFR2	42.3 ± 3.71

Mean ± standard deviation, n = 3.

The inhibitory effect of tasurgratinib on the autophosphorylation of FGFR was investigated by western blotting using human gastric cancer-derived SNU-16 cells with *FGFR2* gene amplification. The IC_{50} of tasurgratinib (n = 3, mean ± standard deviation) was 1.34 ± 0.647 nmol/L.

3.1.3 Inhibitory effect on the proliferation of malignant tumor-derived cell lines

3.1.3.1 Cholangiocarcinoma-derived cells

3.1.3.1.1 *In vivo* (CTD 4.2.1.1.15)

The inhibitory effect of tasurgratinib on tumor growth was investigated using nude mice (n = 6 or 7/group) subcutaneously transplanted with fragments of CC6204 tumor tissues derived from patients with cholangiocarcinoma with *FGFR2-BicC family RNA binding protein 1* (*BICC1*) gene fusion.[10)] The study started at the time point when the mean tumor volume reached 193 mm^3 (Day 0), and tasurgratinib 3.8, 12, or 38 mg/kg was administered orally QD on Days 0 to 14 to calculate the tumor volume. The results showed a statistically significant suppression of tumor growth in the tasurgratinib 12 and 38 mg/kg groups, compared with the control (distilled water) group, on Day 14 (Figure 1).

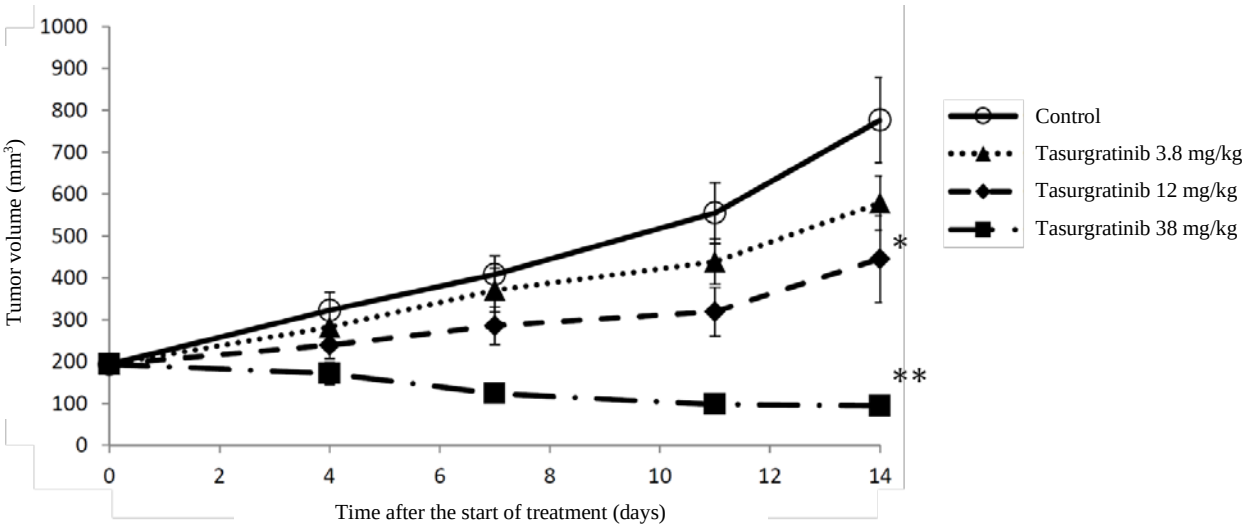


Figure 1. Inhibitory effect of tasurgratinib on tumor growth in nude mice subcutaneously transplanted with CC6204 tumor tissue fragments

n = 6 or 7; mean ± standard error; *, $P < 0.05$ versus control; **, $P < 0.001$ versus control (Dunnett's multiple comparison test).

3.1.3.2 Cell lines derived from malignant tumors other than cholangiocarcinoma

3.1.3.2.1 *In vitro* (CTD 4.2.1.1.5, 4.2.1.1.8, and 4.2.1.1.9)

The inhibitory effect of tasurgratinib on the proliferation of human umbilical vein endothelial cells (HUVECs) in the presence of basic FGF or VEGF was investigated using the activity of reductase derived from viable cells as an indicator. The IC_{50} values of tasurgratinib (n = 3, mean ± standard deviation) in the presence of basic FGF and VEGF were 21.5 ± 1.32 and 284 ± 23.5 nmol/L, respectively.

The inhibitory effect of tasurgratinib on the proliferation of 4 human malignant tumor-derived cell lines with *FGFR* gene abnormalities was investigated using the activity of reductase derived from viable cells as an indicator. Table 8 shows the IC_{50} values of tasurgratinib.

[10)] Fusion of exon 17 of the *FGFR*2 gene and exon 10 of the *BICC1* gene.

Table 8. Inhibitory effect of tasurgratinib on the proliferation of various cell lines

Cell line	Origin	*FGFR* gene abnormality	IC_{50} (nmol/L)
SNU-16	Gastric cancer	*FGFR2* gene amplification	5.74 ± 0.844
NCI-H1581	Non-small cell lung cancer	*FGFR1* gene amplification	7.24 ± 0.961
AN3 CA	Endometrial cancer	*FGFR2* gene mutation (K310R and N549K[*1])	17.3 ± 5.25
RT112/84	Bladder cancer	*FGFR3-TACC3* gene fusion[*]2	34.4 ± 3.62

Mean ± standard deviation; n = 3; *1, substitution of lysine at position 310 by arginine, and substitution of asparagine at position 549 by lysine; *2, fusion of exon 18 of the *FGFR3* gene and exon 11 of the *TACC3* gene.

The inhibitory effect of tasurgratinib on the proliferation of mouse fetal fibroblast-derived NIH/3T3 cell lines transfected with various *FGFR2* gene fusions was investigated using the activity of reductase derived from viable cells as an indicator. Table 9 shows the IC_{50} values of tasurgratinib.

Table 9. Inhibitory effect of tasurgratinib on the proliferation of NIH/3T3 cell lines

Transfected *FGFR* gene fusion	IC_{50} (nmol/L)
FGFR2-AHCYL1[*1]	0.918, 0.662
FGFR2-BICC1 type1[*2]	1.87, 3.17
FGFR2-BICC1 type2[*3]	16.2, 16.1
FGFR2-TXLNA[*4]	4.26, 1.20
FGFR2-KCTD1[*5]	0.845, 5.01

n = 2 (individual data). *1, fusion of exon 17 of the *FGFR2* gene and exon 5 of the *AHCYL1* gene; *2, fusion of exon 17 of the *FGFR2* gene and exon 3 of the *BICC1* gene; *3, fusion of exon 17 of the *FGFR2* gene and exon 18 of the *BICC1* gene; *4, fusion of exon 17 of the *FGFR2* gene and exon 6 of the *TXLNA* gene; *5, fusion of exon 17 of the *FGFR2* gene and exon 2 of the *KCTD1* gene.

3.1.3.2.2 *In vivo* (CTD 4.2.1.1.10, 4.2.1.1.11, and 4.2.1.1.12)

The inhibitory effect of tasurgratinib on tumor growth was investigated using nude mice (n = 6/group) subcutaneously transplanted with SNU-16 or NCI-H1581 cells. The study started on the day when tumor volume reached a certain level (158.8-210.3 mm^3 for SNU-16 and 118.6-176.5 mm^3 for NCI-H1581) (Day 1), and tasurgratinib 4.8, 9.6, 19, or 38 mg/kg was administered orally QD on Days 1 to 14 to calculate the tumor volume. Table 10 shows the tumor volume and treated/control ratio (T/C)[11] on Day 15.

Table 10. Inhibitory effect of tasurgratinib on tumor growth in nude mice subcutaneously transplanted with various cell lines

Cell line	Dose (mg/kg)	Tumor volume (mm^3)	T/C (%)
SNU-16	4.8	645.3 ± 146.1[*1]	50.8 ± 16.9[*1]
	9.6	416.0 ± 138.9[*2]	25.8 ± 15.0[*2]
	19	300.1 ± 47.0[*2]	13.0 ± 4.45[*2]
	38	179.5 ± 31.3[*2]	−0.0201 ± 3.43[*2]
NCI-H1581	4.8	710.6 ± 277.6[*2]	36.5 ± 17.6[*2]
	9.6	415.5 ± 97.9[*2]	17.4 ± 6.49[*2]
	19	224.3 ± 62.8[*2]	5.07 ± 3.29[*2]
	38	151.8 ± 23.2[*2]	0.447 ± 0.876[*2]

Mean ± standard deviation, n = 6. *1, $P < 0.001$ versus control (Dunnett's multiple comparison test); *2, $P < 0.0001$ versus control (Dunnett's multiple comparison test).

The inhibitory effect of tasurgratinib on tumor growth was investigated using nude mice (n = 6/group) subcutaneously transplanted with NIH/3T3 cells transfected with *FGFR2-KCTD1* gene fusion. The study started on the day when the average tumor volume reached 129 mm^3 (Day 1), tasurgratinib 4.8, 9.6, 19, or

[11] T/C (%) = [{(tumor volume on Day 15 in the tasurgratinib group) − (tumor volume on Day 1 in the tasurgratinib group)} / {(mean tumor volume on Day 15 in the control [distilled water] group) − (mean tumor volume on Day 1 in the control [distilled water] group)}] × 100.

38 mg/kg was administered orally QD on Days 1 to 7 to calculate the tumor volume. The results showed a statistically significant inhibition of tumor growth in all tasurgratinib groups, compared with the control (10 mmol/L HCl) group, on Day 8 ($P < 0.001$ for tasurgratinib 4.8 mg/kg and $P < 0.0001$ for tasurgratinib 9.6, 19, and 38 mg/kg; Dunnett's multiple comparison test for both).

3.2 Secondary pharmacodynamics (CTD 4.2.1.2.1)

The inhibitory effect of tasurgratinib on 86 types of receptors, transporters, and ion channels was investigated using radiolabeled ligands. Tasurgratinib 10 μmol/L inhibited the benzodiazepine receptor, dopamine D1 receptor, 5-HT_{1B} receptor, sigma receptor, and sodium ion channel by ≥50%. Of these, the sigma receptor was inhibited by ≥50% even with tasurgratinib 1.0 μmol/L (i.e., 54.5%).

3.3 Safety pharmacology

3.3.1 Effects on the central nervous system

In a 4-week repeated oral dose toxicity study in rats (n = 6/group) [see Section 5.2], tasurgratinib 1.5, 5.4, or 21 mg/kg was administered orally QD, and effects of tasurgratinib on the central nervous system were investigated by the functional observational battery. Tasurgratinib was found to have no effects.

3.3.2 Effects on the cardiovascular system

3.3.2.1 Effects on hERG potassium current (CTD 4.2.1.3.1)

Effects of tasurgratinib 3, 10, and 30 μmol/L on human ether-a-go-go related gene (hERG) potassium current were investigated using CHO cells transfected with hERG. The IC_{50} of tasurgratinib was >29.4 μmol/L.[12)]

3.3.2.2 Effects on heart rate, blood pressure, and electrocardiogram (CTD 4.2.1.3.2)

A single oral dose of tasurgratinib 30, 100, and 300 mg/kg was sequentially administered to dogs (n = 3), and effects of tasurgratinib on heart rate, blood pressure, and electrocardiogram (PR, QRS, and QTc intervals) were investigated. Tasurgratinib 300 mg/kg increased the heart rate, shortened the PR interval, and prolonged the QTc interval.

In a 4-week repeated oral dose toxicity study in dogs (n = 3 or 5/group) [see Section 5.2], tasurgratinib 1.2, 4.1, or 21 mg/kg was administered orally QD, and effects of tasurgratinib on heart rate and electrocardiogram were investigated. Tasurgratinib was found to have no effects.

The applicant's explanation about the above findings observed with tasurgratinib 300 mg/kg:
Tasurgratinib is unlikely to raise safety concerns during clinical use, given that the plasma C_{max} (86.5 ng/mL) of unbound tasurgratinib following administration of tasurgratinib 300 mg/kg to dogs was higher than the plasma C_{max} (23.4 ng/mL)[13)] of unbound tasurgratinib following administration of tasurgratinib to humans at the recommended clinical dose.

[12)] When tasurgratinib 30 μmol/L was added (actual concentration in the perfusion solution: 29.4 μmol/L), the percent inhibition of hERG potassium current was <50%. Therefore, the IC_{50} of tasurgratinib was determined to be >29.4 μmol/L.

[13)] Calculated based on the C_{max} (372 ng/mL) [see Section 6.2.1.1] and the plasma protein binding rate (93.7%) [see Section 4.2.2] of tasurgratinib on Day 8 after oral administration of tasurgratinib 140 mg QD to Japanese patients in the Japanese phase I study (Study 101).

3.3.3 Effects on the respiratory system

In a 4-week repeated oral dose toxicity study in rats (n = 6/group) [see Section 5.2], tasurgratinib 1.5, 5.4, or 21 mg/kg was administered orally QD, and effects of tasurgratinib on respiratory rate, tidal volume, and minute volume were investigated. Tasurgratinib was found to have no effects.

3.R Outline of the review conducted by PMDA

On the basis of the data submitted and the review presented in the section below, PMDA has concluded that the applicant's explanation about the non-clinical pharmacology of tasurgratinib is acceptable.

3.R.1 Mechanism of action and efficacy of tasurgratinib

The applicant's explanation about the mechanism of action of tasurgratinib and its efficacy in the treatment of biliary tract cancer with *FGFR2* gene fusion:

It has been reported that FGFR family proteins (FGFR1 to FGFR3) all bind to an FGF ligand and are involved in cellular proliferation and other activities via their downstream signaling molecules such as phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) and MAPK (*Cancer Discov*. 2013;3:264-279, *Mol Cancer Res*. 2010;8:1439-1452, etc.).

Fusion of *FGFR* gene with another gene results in the production of FGFR fusion protein, which can constitutively activate its downstream signaling pathways such as MAPK pathway (*Nat Rev Cancer*. 2017;17:318-332, *Int J Mol Sci*. 2020;21:6856). In addition, the following finding suggests that *FGFR* gene fusion is an oncogenic driver of tumor cell proliferation.

- In conditional knock-in mice in which Cre recombinase was designed to induce expression of *FGFR3-transforming acidic coiled-coil containing protein 3* (*TACC3*) gene fusion, intratracheal administration of adenoviral vector that induced expression of Cre recombinase under the control of a cytomegalovirus (CMV)-derived promoter led to development of lung adenocarcinoma (*Oncogene*. 2018;37:6096-6104).

Tasurgratinib inhibits FGFR1 to 3 kinases [see Section 3.1.2] and the phosphorylation of their downstream signaling molecules (ERK, AKT, etc.) (*Mol Cancer Ther*. 2016;15:2630-2639), thus suppressing tumor growth. In addition to the oncogenic mechanism driven by *FGFR* gene fusions, tasurgratinib also suppressed tumor growth in nude mice subcutaneously transplanted with tumor tissue fragments derived from patients with cholangiocarcinoma harboring *FGFR2-BICC1* gene fusion [see Section 3.1.3.1]. In view of these findings, tasurgratinib is expected to have efficacy in the treatment of biliary tract cancer with *FGFR2* gene fusion.

The applicant's explanation about similarities and differences in pharmacological attributes between tasurgratinib and other FGFR inhibitors, pemigatinib and futibatinib, which have been approved in Japan:

Tasurgratinib, pemigatinib, and futibatinib all inhibit the kinase activity of FGFR1 to 3, but they differ in the following points:

- The inhibitory activity of both tasurgratinib and pemigatinib against FGFR4 is weaker than that of futibatinib (*PLoS One*. 2020;15:e0231877, *Cancer Res*. 2020;80:4986-4997, *Mol Cancer Ther*.

2016;15:2630-2639).

- Futibatinib covalently binds to the ATP binding site of FGFR, and pemigatinib non-covalently binds to the ATP binding site of FGFR (*ChemMedChem*. 2019;14:494-500, *Commun Chem*. 2022;5:100). Meanwhile, tasurgratinib non-covalently binds to the ATP binding site as well as the allosteric site of FGFR [see Section 3.1.1].

In addition, tasurgratinib inhibited the proliferation of the NIH/3T3 cell line transfected with the FGFR2 N549K/H mutation (*Cancer Discov*. 2021;11:326-339),[14)] which has been reported as a mutation for acquired resistance to pemigatinib (*NPJ Precis Oncol*. 2021;5:66).

PMDA's view:
PMDA accepted the applicant's explanation. However, knowledge about the pharmacological attributes of tasurgratinib, including similarities and differences in such attributes of tasurgratinib compared with pemigatinib and futibatinib, may be important to predict the efficacy of tasurgratinib in clinical use and to identify eligible patients. The applicant should continue investigations on the above aspects to appropriately provide new findings to healthcare professionals when they become available.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Unless otherwise specified, the doses of tasurgratinib and the concentrations of tasurgratinib and M2 are expressed as those of the free base in this section.

The pharmacokinetics (PK) of tasurgratinib in animals was investigated in dogs and other species. Plasma protein binding, drug-metabolizing enzymes, and transporters of tasurgratinib were investigated using human or animal biological samples.

Tasurgratinib and M2 in dog plasma were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantification: 1 ng/mL and 0.05 ng/mL, respectively). Radioactivity in rat tissues was determined by quantitative whole-body autoradiography (lower limit of quantification: 13.5 ng Eq./g).

4.1 Absorption

4.1.1 Single-dose administration

A single intravenous dose of tasurgratinib 1.5 mg/kg[15)] or a single oral dose of tasurgratinib 1.5, 5.4, or 27 mg/kg[15)] was administered to male dogs, and plasma tasurgratinib concentrations were determined (Table 11). Tasurgratinib exposure following oral administration increased in a generally dose-proportional manner over the dose range studied.

[14)] Asparagine at position 549 substituted by lysine or histidine.
[15)] Dose of Tasurgratinib Succinate.

Table 11. PK parameters of tasurgratinib (male dogs, single intravenous or oral dose administration)

Route of administration	Dose (mg/kg)	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	F*2 (%)
i.v.	1.5	3	-	-	1,237.2 ± 34.5	7.79 ± 0.21	-
p.o.	1.5	3	73.2 ± 4.33	3.33 (2, 4)	793.5 ± 95.2	5.66 ± 0.08	65.3
	5.4	5	219 ± 17.1	2.40 (2, 4)	2,797.0 ± 141.7	6.64 ± 0.51	63.9
	27	5	1,010 ± 108	1.30 (0.5, 2)	13,144.6 ± 1,510.9	8.58 ± 0.90	60.1

Mean ± standard error. *1, median (minimum, maximum); *2, absolute bioavailability calculated based on the mean AUC_{inf}; -, not calculated.

4.1.2 Repeated-dose administration

Repeated oral doses of tasurgratinib 0.5, 1, or 2 mg/kg[15)] were administered QD for 13 weeks to male and female dogs, and plasma tasurgratinib and M2 concentrations were determined (Table 12). No clear sex differences were noted in the tasurgratinib exposure. Tasurgratinib exposure increased in a generally dose-proportional manner, and did not tend to increase with repeated doses.

Table 12. PK parameters of tasurgratinib (male and female dogs, 13-week repeated oral dose administration)

Measurement day	Dose (mg/kg)	Analyte	C_{max} (ng/mL)		t_{max}* (h)		AUC_{24h} (ng·h/mL)	
			Males	Females	Males	Females	Males	Females
Day 1	0.5	Tasurgratinib	22.3 ± 2.63	28.3 ± 3.46	4 (4, 8)	4 (2, 4)	312 ± 4.73	321 ± 4.62
		M2	0.181 ± 0.0182	0.261 ± 0.120	2 (2, 4)	2 (2, 2)	1.49 ± 0.182	2.22 ± 0.975
	1	Tasurgratinib	44.1 ± 5.35	51.0 ± 11.6	8 (2, 8)	4 (2, 4)	661 ± 78.0	697 ± 41.4
		M2	0.368 ± 0.199	0.572 ± 0.236	2 (2, 2)	2 (2, 4)	4.39 ± 1.38	7.32 ± 3.21
	2	Tasurgratinib	86.5 ± 23.9	96.0 ± 4.80	4 (2, 8)	4 (4, 4)	1,230 ± 403	1,170 ± 176
		M2	0.957 ± 0.209	0.795 ± 0.0277	2 (2, 4)	4 (2, 4)	11.1 ± 5.33	8.68 ± 3.44
Day 91	0.5	Tasurgratinib	32.9 ± 3.00	30.6 ± 6.98	4 (4, 4)	4 (4, 4)	408 ± 9.87	379 ± 35.4
		M2	0.236 ± 0.0610	0.205 ± 0.0487	2 (2, 2)	4 (2, 4)	1.89 ± 0.179	2.45 ± 0.256
	1	Tasurgratinib	64.4 ± 10.2	69.1 ± 17.1	4 (2, 8)	4 (2, 4)	844 ± 62.6	932 ± 135
		M2	0.413 ± 0.124	0.624 ± 0.346	2 (2, 4)	4 (4, 4)	5.73 ± 1.87	7.51 ± 3.31
	2	Tasurgratinib	143 ± 49.2	101 ± 6.01	2 (2, 4)	4 (4, 8)	1,370 ± 512	1,470 ± 251
		M2	0.960 ± 0.351	0.830 ± 0.0799	2 (2, 2)	4 (2, 8)	8.41 ± 3.50	10.0 ± 3.18

Mean ± standard deviation. n = 3. *, median (minimum, maximum).

4.1.3 *In vitro* membrane permeability

The *in vitro* membrane permeability of tasurgratinib has not been investigated. In view of the absorption rate (68%[16)]) of tasurgratinib following its oral administration in humans, the membrane permeability of tasurgratinib is moderate, according to the applicant.

4.2 Distribution

4.2.1 Tissue distribution

A single oral dose of ^{14}C-labeled tasurgratinib 3 mg/kg was administered to male pigmented and albino rats, and tissue distribution of radioactivity was investigated. The radioactivity was extensively distributed in tissues of pigmented and albino rats. In most of the tissues, the radioactivity concentration peaked at 4 to 12 hours post-dose. In albino rats, the maximum tissue radioactivity concentrations in (a) the bile duct, (b) kidney (inner cortex and outer cortex), (c) liver, (d) adrenal gland (cortex and medulla), (e) spleen, (f) thyroid, and (g) pituitary ((a) 1,910 ng Eq./g, (b) 2,100 ng Eq./g [inner cortex] and 1,030 ng Eq./g [outer cortex], (c) 1,750 ng Eq./g, (d) 1,520 ng Eq./g [cortex] and 1,120 ng Eq./g [medulla], (e) 1,030 ng Eq./g, (f) 1,450 ng Eq./g,

16) Estimated based on the fecal excretion (32%) of unchanged tasurgratinib in humans [see Section 6.2.2.1].

and (g) 1,190 ng Eq./g) were particularly higher than the maximum radioactivity concentration in blood (84.0 ng Eq./g). The tissue distribution of radioactivity in pigmented rats was generally similar to that in albino rats, except for the pigmented skin and uvea, and the radioactivity concentration in each tissue was lower in pigmented rats than in albino rats. In albino rats, the radioactivity concentrations in most of the tissues fell below the lower limit of quantification within 168 hours post-dose. In pigmented rats, however, the radioactivity was detected even at 672 hours post-dose in the aortic wall, meninges, pigmented skin, and uvea/retina.

While the above results suggested that tasurgratinib or its metabolites bind to melanin, no toxicological findings attributable to the distribution of tasurgratinib or its metabolites in melanin-containing tissues were observed in repeated-dose toxicity studies in rats and dogs [see Section 5.2]. In view of this, the applicant explained that safety concerns associated with the distribution of tasurgratinib or its metabolites in melanin-containing tissues are unlikely to occur during the clinical use of tasurgratinib. The safety of tasurgratinib for the eyes and skin is discussed in Sections "7.R.3.4 Retinal disorder," "7.R.3.5 Eye disorders (except for retinal disorder)," and "7.R.3.7 Skin disorders."

4.2.2 Plasma protein binding

Tasurgratinib (100-3,000 ng/mL) was incubated with mouse, rat, dog, and human plasma at 4°C (mouse and rat plasma) or 37°C (dog and human plasma) for 48 hours, and the plasma protein binding of tasurgratinib was investigated using equilibrium dialysis. The plasma protein binding rates of tasurgratinib in mice, rats, dogs, and humans were 96.8% to 97.1%, 96.7% to 96.9%, 91.6% to 92.6%, and 93.2% to 94.3%, respectively.

M2 (30-1,000 ng/mL) was incubated with human plasma at 37°C for 48 hours, and the plasma protein binding of M2 was investigated using equilibrium dialysis. The plasma protein binding rate of M2 in humans was 89.3% to 90.5%.

Tasurgratinib or M2 (both 30-300 ng/mL) was incubated with human serum albumin (40 mg/mL), human α1-acid glycoprotein (1 mg/mL), or human γ-globulin (12 mg/mL) at 37°C for 24 hours, and the binding of tasurgratinib or M2 to human serum albumin, human α1-acid glycoprotein, and human γ-globulin was investigated using equilibrium dialysis. The binding rates of (a) tasurgratinib and (b) M2 to human serum albumin, human α1-acid glycoprotein, and human γ-globulin were (a) 71.1% to 72.4%, 30.9% to 37.3%, and 36.5% to 39.0%, respectively, and (b) 73.5% to 74.8%, 45.0% to 51.7%, and 42.6% to 45.9%, respectively. On the basis of the above, the applicant explained that tasurgratinib and M2 mainly bind to serum albumin in human plasma.

4.2.3 Distribution in blood cells

Tasurgratinib or M2 (both 30-300 ng/mL) was incubated with mouse, rat, dog, and human blood at 37°C for 30 minutes, and the distribution of tasurgratinib and M2 in blood cells was investigated. The blood/plasma ratio of (a) tasurgratinib and (b) M2 in mice, rats, dogs, and humans was (a) 1.23 to 1.29, 0.952 to 1.02, 0.929

to 0.966, and 1.06 to 1.14, respectively, and (b) 1.14 to 1.30, 1.12 to 1.16, 0.992 to 1.01, and 1.14 to 1.16, respectively.

4.2.4 Placental and fetal transfer

The placental and fetal transfer of tasurgratinib has not been investigated. The applicant explained that tasurgratinib may cross the placenta into the fetus, considering that tasurgratinib was found to be teratogenic in an embryo-fetal development study in rats [see Section 5.5].

4.3 Metabolism

4.3.1 *In vitro*

Tasurgratinib (5 μmol/L) was incubated with mouse, rat, dog, and human hepatocytes at 37°C for 1 to 4 hours, and metabolites of tasurgratinib were investigated. No human-specific metabolites were detected. Metabolites detected in human hepatocytes were M1 (*N*-oxidized form), M2 (dealkylated form), M3 (carboxylated form), M4 (oxidized form), and M5 (hydrolyzed form).

The applicant's explanation based on the investigation results below:
CYP3A4 and CYP4F12 are considered to be mainly involved in the metabolism of tasurgratinib in humans, while CYP4F12 is mainly involved in the metabolism of tasurgratinib to M2. CYP2J2, CYP3A4, and CYP4F12 are considered to be mainly involved in the metabolism of M2. CYP3A-mediated pharmacokinetic interactions of tasurgratinib are described in Section "6.2.3 Drug interaction study."

- Tasurgratinib (1 μmol/L) was incubated with recombinant human CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2J2, CYP3A4, CYP3A5, and CYP4F12) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 30 minutes (15 minutes for CYP4F12), and CYP isoforms involved in the metabolism of tasurgratinib were investigated. The residual rates of tasurgratinib in the presence of CYP2J2, CYP3A4, and CYP4F12 were 76.3%, 10.9%, and 43.9%, respectively, and those in the presence of other CYP isoforms investigated were ≥85.2%.
- Tasurgratinib (1 μmol/L) was incubated with recombinant human CYP isoforms (CYP2J2, CYP3A4, and CYP4F12) in the presence of NADPH at 37°C for 15 minutes (5 minutes for CYP4F12), and CYP isoforms involved in the metabolism of tasurgratinib to M2 were investigated. The formation rates of M2 in the presence of CYP2J2, CYP3A4, and CYP4F12 were 0.0954, 0.0116, and 3.15 pmol/min/pmol CYP, respectively.
- M2 (0.1 μg/mL) was incubated with recombinant human CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2J2, CYP3A4, CYP3A5, and CYP4F12) in the presence of NADPH at 37°C for 30 minutes, and CYP isoforms involved in the metabolism of M2 were investigated. The residual rates of M2 in the presence of CYP2J2, CYP3A4, and CYP4F12 were 68.4%, 49.5%, and 53.5%, respectively, and those in the presence of other CYP isoforms investigated were ≥91.7%.

4.3.2 *In vivo*

A single oral dose of ^{14}C-labeled tasurgratinib 3 mg/kg was administered to non-bile duct-cannulated or bile duct-cannulated male rats, and tasurgratinib metabolites in plasma, urine, bile, and feces were investigated. The following results were obtained:

- In plasma collected from non-bile duct-cannulated male rats up to 6 hours post-dose, unchanged tasurgratinib and M7 (demethylated form) were mainly detected (accounting for 19.2% and 13.6%, respectively, of the total radioactivity in plasma).
- In urine collected from non-bile duct-cannulated male rats up to 24 hours post-dose, a +2O+2H form of M6 (hydrolyzed form) and M7 were mainly detected (accounting for 0.30% and 0.74%, respectively, of the administered radioactivity).
- In bile collected from bile duct-cannulated male rats up to 24 hours post-dose, a demethylated form of M3 and M7 were mainly detected (accounting for 5.62% and 6.68%, respectively, of the administered radioactivity).
- In feces collected from non-bile duct-cannulated male rats up to 48 hours post-dose, unchanged tasurgratinib, a demethylated form of M3, M7, a +O-2H form of M7, and a dicarboxylate metabolite of M7 were mainly detected (accounting for 13.6%, 8.63%, 11.1%, 14.5%, and 8.12%, respectively, of the administered radioactivity).

4.4 Excretion

4.4.1 Excretion in urine, feces, and bile

A single oral dose of ^{14}C-labeled tasurgratinib 3 mg/kg was administered to non-bile duct-cannulated or bile-duct cannulated male rats, and urinary, biliary, and fecal excretion rates of tasurgratinib were investigated. In non-bile duct-cannulated male rats, the urinary and fecal excretion rates of radioactivity (relative to the administered radioactivity) up to 168 hours post-dose were 4.02% and 96.3%, respectively. In bile duct-cannulated male rats, the urinary, fecal, and biliary excretion rates of radioactivity (relative to the administered radioactivity) up to 72 hours post-dose were 34.8%, 17.8%, and 38.0%, respectively.

4.4.2 Excretion in milk

Transfer of tasurgratinib into milk has not been investigated. In view of the physicochemical properties of tasurgratinib (pKa, 4.1 and 8.8; log *P* value, 4.0), the applicant explained that tasurgratinib may be excreted in milk.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

In view of the investigation results below, the applicant explained that tasurgratinib may cause pharmacokinetic interactions mediated by its inhibition of CYP3A and CYP4F12 in clinical settings.

- Tasurgratinib (0.3-100 μmol/L), M2 (0.3-100 μmol/L), or (*R*)-M9 (oxidized derivative of M2) (0.1-

10 μmol/L) was incubated with human liver microsomes in the presence of substrates[17] of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) and NADPH to investigate the inhibitory effects of tasurgratinib, M2, and (*R*)-M9 on the CYP isoforms. Tasurgratinib inhibited the metabolism of substrates of CYP2D6 and CYP3A, with an IC_{50} of 95.0 and 16.4 μmol/L,[18] respectively. M2 inhibited the metabolism of substrates of CYP2C9, CYP2C19, CYP2D6, and CYP3A, with an IC_{50} of 77.5, 93.0, 82.0, and 22.1 μmol/L,[19] respectively. In contrast, tasurgratinib and M2 did not clearly inhibit the metabolism of substrates of other CYP isoforms. (*R*)-M9 did not show a clear inhibitory effect on any of the CYP isoforms investigated.

- Tasurgratinib (0.3-100 μmol/L), M2 (0.3-100 μmol/L), or (*R*)-M9 (1-10 μmol/L) was pre-incubated with human liver microsomes in the presence of NADPH, and then incubated with substrates[20] of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) to investigate the time-dependent inhibitory effects of tasurgratinib, M2, and (*R*)-M9 on the CYP isoforms. Tasurgratinib, M2, and (*R*)-M9 did not clearly inhibit the metabolism of substrates in a time-dependent manner for any of the CYP isoforms investigated.
- Tasurgratinib or M2 (both 0.03-30 μmol/L) was incubated with recombinant human CYP isoforms (CYP2J2 and CYP4F12) in the presence of substrates[21] of CYP isoforms (CYP2J2 and CYP4F12) and NADPH to investigate the inhibitory effects of tasurgratinib and M2 on the CYP isoforms. Tasurgratinib inhibited the metabolism of substrates of CYP4F12, with an IC_{50} of 0.446 μmol/L. In contrast, tasurgratinib did not clearly inhibit the metabolism of substrates of CYP2J2. M2 inhibited the metabolism of substrates of CYP2J2 and CYP4F12, with an IC_{50} of 25.1 and 0.827 μmol/L, respectively.
- Tasurgratinib or M2 (both 10 μmol/L) was pre-incubated with recombinant human CYP isoforms (CYP2J2 and CYP4F12) in the presence of NADPH, and then incubated with substrates[21] of CYP isoforms (CYP2J2 and CYP4F12) to investigate the time-dependent inhibitory effects of tasurgratinib and M2 on the CYP isoforms. Tasurgratinib and M2 did not clearly inhibit the metabolism of substrates in a time-dependent manner for either of the CYP isoforms investigated.

4.5.2 Enzyme induction

In view of the investigation results below, the applicant explained that tasurgratinib may cause pharmacokinetic interactions mediated by its induction of CYP1A2, CYP2B6, and CYP3A in clinical settings.

- Tasurgratinib (0.3-3 μmol/L) was incubated with human cryopreserved hepatocytes for 3 days, and the messenger ribonucleic acid (mRNA) expression of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) was investigated. Tasurgratinib increased the mRNA expression of CYP1A2, CYP2B6, and CYP3A4 by up to 10.72-, 4.47-, and 10.50-fold, respectively, those with the vehicle control, and to ≤11.6%,

[17] Substrates used for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were phenacetin, bupropion, amodiaquine, diclofenac, S-mephenytoin, and bufuralol, respectively, and substrates of CYP3A used were testosterone, midazolam, and nifedipine (midazolam and testosterone in the investigation of (*R*)-M9).

[18] IC_{50} for CYP3A is the value for midazolam used as a substrate of CYP3A. The IC_{50} for nifedipine or testosterone used as a substrate of CYP3A was 27.9 and 48.0 μmol/L, respectively.

[19] IC_{50} for CYP3A is the value for midazolam used as a substrate of CYP3A. The IC_{50} for nifedipine or testosterone used as a substrate of CYP3A was 31.6 and 62.4 μmol/L, respectively.

[20] Substrates used for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 were phenacetin, bupropion, amodiaquine, diclofenac, S-mephenytoin, and bufuralol, respectively, and substrates of CYP3A used were testosterone, midazolam, and nifedipine (only midazolam in the investigation of (*R*)-M9).

[21] The substrate used for CYP2J2 and CYP4F12 was terfenadine.

≤26.3%, and ≤10.9%, respectively, of those with the respective positive controls.[22)]

- M2 (0.3-10 μmol/L) was incubated with human cryopreserved hepatocytes for 3 days, and the mRNA expression of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) was investigated. M2 increased the mRNA expression of CYP1A2, CYP2B6, and CYP3A4 by up to 1.44-, 1.91-, and 2.96-fold, respectively, those with the vehicle control, and to <20% of those with the respective positive controls[22)] for all.

4.5.3 Transporters

The following investigation results suggested that tasurgratinib and M2 are substrates of P-glycoprotein (P-gp):

- P-gp-mediated transport of ^{14}C-labeled tasurgratinib (1-10 μmol/L[23)]) was investigated using a porcine renal epithelial cell-derived LLC-PK1 cell line engineered to express human P-gp. The ratio of the efflux ratio of ^{14}C-labeled tasurgratinib in a P-gp-expressing cell line to that in a non-expressing cell line was 3.50 in the presence of a P-gp inhibitor (verapamil 30 μmol/L) and 12.58 to 16.61 in the absence of the inhibitor.
- Breast cancer resistance protein (BCRP)-mediated transport of ^{14}C-labeled tasurgratinib (1 μmol/L) was investigated using a dog kidney-derived MDCKII cell line engineered to express human BCRP. The ratio of the efflux ratio of ^{14}C-labeled tasurgratinib in a BCRP-expressing cell line to that in a non-expressing cell line was 1.00 to 1.07.
- Organic anion transporting polypeptide (OATP)1B1- and OATP1B3-mediated transport of ^{14}C-labeled tasurgratinib (1 and 30 μmol/L) was investigated using a human fetal kidney-derived HEK293 cell line engineered to express human OATP1B1 or OATP1B3. No clear differences were observed in the uptake of ^{14}C-labeled tasurgratinib between the OATP1B1/OATP1B3-expressing and non-expressing cell lines.
- P-gp- and BCRP- mediated transport of M2 (10 μmol/L)was investigated using a human colon cancer-derived Caco-2 cell line. The efflux ratios of M2 in the presence of (a) a P-gp inhibitor (verapamil 30 μmol/L) and (b) a BCRP inhibitor (Ko143 1.0 μmol/L) were (a) 1.8 and (b) 10.2, respectively, and the efflux ratio of M2 without these inhibitors was 12.4.
- OATP1B1- and OATP1B3-mediated transport of M2 (1 and 10 μmol/L) was investigated using a HEK293 cell line engineered to express human OATP1B1 or OATP1B3. No clear differences were noted in the uptake of M2 between the OATP1B1/OATP1B3-expressing and non-expressing cell lines.

In view of the investigation results below, the applicant also explained that tasurgratinib may cause pharmacokinetic interactions mediated by its inhibition of P-gp, BCRP, and multidrug and toxin extrusion (MATE)1, as well as inhibition of MATE1 by M2 in clinical settings.

- The inhibitory effect of tasurgratinib (3.9-13 μmol/L for P-gp, and 13-39 μmol/L for BCRP) or M2 (10-30 μmol/L for P-gp, and 30-100 μmol/L for BCRP) on the transport of the substrate[24)] by each transporter was investigated using an LLC-PK1 cell line engineered to express human P-gp and an MDCKII cell line engineered to express human BCRP. Since tight junctions could not be maintained at

[22)] Positive controls used for CYP1A2, CYP2B6, and CYP3A4 were omeprazole (50 μmol/L), phenobarbital (750 μmol/L), and rifampicin (20 μmol/L), respectively.
[23)] The investigation in the presence of the P-gp inhibitor was conducted with ^{14}C-labeled tasurgratinib 3 μmol/L.
[24)] Substrates used for P-gp and BCRP were ^{3}H-labeled digoxin (1 μmol/L) and ^{3}H-labeled prazosin (1 μmol/L), respectively.

concentrations exceeding the maximum concentration investigated, the IC_{50} of tasurgratinib for P-gp and BCRP could not be calculated. However, in view of the estimated tasurgratinib concentration (953 μmol/L) in the gastrointestinal tract following administration of tasurgratinib at the proposed dosage and administration, tasurgratinib may inhibit P-gp and BCRP in the gastrointestinal tract.[25)]

- The inhibitory effects of tasurgratinib and M2 (both 0.3-30 μmol/L[26)]) on the transport of the substrate[27)] by each transporter were investigated using a human HEK293 cell line engineered to express organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K. The results showed that (a) tasurgratinib and (b) M2 inhibited the transport of substrates of OCT1, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K, with an IC_{50} of (a) 0.888, 5.53, 14.6, 6.43, 0.0870, and 5.99 μmol/L, respectively, and (b) 0.332, 3.85, 18.6, 7.43, 0.0287, and 6.76 μmol/L, respectively.

4.R Outline of the review conducted by PMDA

On the basis of the data submitted and the review presented in the section below, PMDA has concluded that the applicant's explanation about the non-clinical pharmacokinetics of tasurgratinib is acceptable.

4.R.1 Pharmacokinetic interactions

The applicant's explanation about pharmacokinetic interactions of tasurgratinib:

In vitro study results suggested that tasurgratinib may cause pharmacokinetic interactions mediated by its inhibition or induction of the metabolic enzymes and transporters, listed below, in clinical settings [see Sections 4.5.1, 4.5.2, and 4.5.3]. However, considering that no particular safety concerns about the concomitant use of tasurgratinib with substrates of these metabolic enzymes or transporters were suggested in a global phase II study (Study 201), concomitant use with the substrates is unlikely to raise problems during the clinical use of tasurgratinib.

- Induction of CYP1A2, CYP2B6, and CYP3A by tasurgratinib
- Inhibition of CYP3A, CYP4F12, P-gp, BCRP, and MATE1 by tasurgratinib, and inhibition of MATE1 by M2

In vitro study results also showed that tasurgratinib and M2 are substrates of P-gp [see Section 4.5.3]. However, considering that no particular safety concerns about the concomitant use of tasurgratinib with P-gp inhibitors were suggested in the global phase II study (Study 201), concomitant use with P-gp inhibitors is unlikely to raise problems during the clinical use of tasurgratinib.

Although CYP4F12 is involved in the metabolism of tasurgratinib [see Section 4.3.1], typical inhibitors and inducers of CYP4F12 have not been identified. In view of this, the applicant considers it unnecessary to provide precautions regarding CYP4F12-mediated pharmacokinetic interactions of tasurgratinib.

[25)] Using the maximum concentration investigated in *in vitro* studies as the IC_{50} of tasurgratinib for P-gp and BCRP (13 and 39 μmol/L, respectively), the risk of pharmacokinetic interactions during the clinical use of tasurgratinib was assessed.

[26)] The investigation for MATE1 was conducted at 0.01 to 1 μmol/L.

[27)] Substrates used for OAT1 and OAT3 were ^{3}H-labeled *p*-aminohippuric acid (1 μmol/L) and ^{3}H-labeled estrone sulfate conjugate (0.05 μmol/L), respectively, the substrate used for OATP1B1 and OATP1B3 was ^{3}H-labeled estradiol-17β-glucuronide (0.05 μmol/L), and substrates used for OCT1, OCT2, MATE1, and MATE2-K were ^{14}C-labeled metformin (10 μmol/L).

PMDA's view:

PMDA largely accepted the applicant's explanation. However, the above *in vitro* study results of pharmacokinetic interactions of tasurgratinib and M2 are important to ensure the proper use of tasurgratinib. Therefore, the applicant should appropriately provide the currently available information to healthcare professionals through the package insert, and continue collecting relevant information to appropriately inform them of any useful information when it becomes available.

5. Toxicology and Outline of the Review Conducted by PMDA

Unless otherwise specified, the doses and concentrations of tasurgratinib are expressed as tasurgratinib succinate in this section.

5.1 Single-dose toxicity

No single-dose toxicity studies of tasurgratinib were conducted. The approximate lethal dose and acute toxicity of tasurgratinib were evaluated based on the results of the 2-week repeated oral dose toxicity studies in rats (CTD 4.2.3.2.1) and dogs (CTD 4.2.3.2.4). No deaths were observed up to the maximum dose in either of these animal species. The approximate lethal oral dose was determined to be >300 mg/kg[28)] in rats and >30 mg/kg[28)] in dogs. No acute toxicities were observed in rats. In dogs, the main acute toxicities observed were vomiting, mucous stools, and watery stools at 30 mg/kg.[28)]

5.2 Repeated-dose toxicity

Four- and 13-week repeated-dose toxicity studies in rats and dogs were conducted (Table 13). The main toxicity findings observed in both rats and dogs were death associated with systemic toxicity, calcareous deposits in organs/tissues throughout the body, increased bone resorption, osteochondral dysplasia, increased blood inorganic phosphorus/ALP, atrophy/opacity of the corneal epithelium, abnormally long fur, and atrophy of the stratified epithelium of the limbs and tongue. In addition, increased blood calcium, incisor dysplasia, and atrophy of the mammary gland were observed in rats, and degeneration/necrosis of the mucosa of the small/large intestine, arterial fibrinoid necrosis, atrophy of the mucosal epithelium of the gingiva/esophagus and the stratified epithelium of the nail bed/paw pads/tongue, atrophy of the epidermis, atrophy of the epithelium of the salivary gland/lacrimal gland/mammary gland, vacuolation of the epithelium in the gastric mucosa/pancreatic duct/renal tubules/epididymis, vacuolation-related abnormalities in renal function parameters, and increased secretion of the gastric mucosa in dogs.

The applicant explained that although it may be attributable to the inhibitory effect of tasurgratinib on FGFR, because FGFR is involved in tooth formation (*Development*. 2010;137:3743-3752), the incisor dysplasia in rats is considered to be a change specific to rats with permanently growing incisors.

[28)] Expressed as free base.

In 13-week repeated-dose toxicity studies in (a) rats and (b) dogs, the no observed adverse effect level (NOAEL) was determined to be (a) 0.6 mg/kg/day and (b) 0.5 mg/kg/day. The AUC_{24h} of tasurgratinib following repeated-dose administration at these doses was (a) 34.1 ng·h/mL (males) and 67.9 ng·h/mL (females), and (b) 408 ng·h/mL (males) and 379 ng·h/mL (females), all of which were <1-fold the human exposure.[29)]

Table 13. Repeated-dose toxicity studies

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Male and female rats (Wistar)	p.o.	4 weeks + 4-week recovery	0[*1], 2, 7, 27	Death 27: 1/10 (females) Decreased body weight/food consumption; sepsis; abnormally long fur; emaciation; yellowish-white nodes in the aorta; yellowish-white discolored area in the heart; reduced thymus size; limb swelling; white area in the spine; osteochondral dysplasia of the femur/sternum; increased focal bone resorption of the femur; incisor dysplasia; atrophy of the epithelium of the cornea; atrophy of the stratified epithelium of the tongue; atrophy of the squamous epithelium of limbs; calcareous deposits in the stomach/kidney/heart/aorta/spine/esophagus/large intestine. Surviving animals ≥2: Increased blood inorganic phosphorus; calcareous deposits in the cornea (males and females). ≥7: Corneal opacity; incisor dysplasia; atrophy of the epithelium of the cornea (males and females); atrophy of the squamous epithelium of limbs (males); calcareous deposits in the kidney (females). 27: Abnormally long fur; finger swelling; decreased body weight/weight gain/food consumption; increased platelet count/reticulocyte count; increased blood calcium/AST/ALP; decreased blood total protein/albumin/A/G ratio; red foci in the glandular stomach; limb swelling; white area in the spine; osteochondral dysplasia of the femur/sternum; increased focal bone resorption of the femur; atrophy of the stratified epithelium of the tongue; calcareous deposits in the stomach/heart/aorta/limbs/spinal cord/spine/esophagus/lingual artery (males and females); calcareous deposits in the kidney/lung/duodenum (males); abnormal gait; emaciation; white discoloration/white foci in the aorta; rib thickening; creamy/granular substance in joints; limb hemorrhage; spine deformation; osteochondral dysplasia of the rib; atrophy of the squamous epithelium of limbs; calcareous deposits in the limb joint (females).	-	4.2.3.2.2
				After the end of the recovery period[*2] ≥7: Corneal opacity; dysplasia/distal persistence of the incisor (males and females); calcareous deposits in the cornea/stomach (males); calcareous deposits in the kidney (females). 27: White discoloration of the incisor; limb swelling; white area in the spine; calcareous deposits in the aorta/limbs/spinal cord/spine/lingual artery (males and females); calcareous deposits in the kidney (males); white discoloration/white foci in the aorta; creamy joints; increased focal bone resorption of the femur;		

[29)] Mean AUC_{24h} (4,800 ng·h/mL) of tasurgratinib following oral administration of tasurgratinib 140 mg QD in patients with advanced solid cancers on Day 8 in the Japanese phase I study (Study 101) [see Section 6.2.1.1].

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
				calcareous deposits in the cornea/stomach/heart artery/pancreatic artery/joints/mesenteric artery (females).		
Male and female rats (Sprague Dawley)	p.o.	13 weeks	0[*1], 0.6, 2, 5	≥2: Increased blood inorganic phosphorus; incisor dysplasia (males); decreased blood total protein/albumin/globulin (females). 5: Discoloration/breakage/loss/overgrowth of teeth; nail elongation; decreased weight gain/food consumption; corneal opacity; colored foci in the lung; osteochondral dysplasia of the sternum/vertebrae; atrophy of the epithelium of the cornea and the stratified epithelium of the tongue and limbs (males and females); tail induration; increased blood calcium/total cholesterol; decreased blood albumin; spine deformation; osteochondral dysplasia of the femur; atrophy of the mammary gland; calcareous deposits in the trachea/renal papilla/aorta/cornea/spine (males); increased blood inorganic phosphorus; decreased blood A/G ratio; increased blood ALP; incisor dysplasia (females).	0.6	4.2.3.2.3
Male and female dogs (beagle)	p.o.	4 weeks + 4-week recovery	0[*1], 1.5, 5.4, 27	Death and premature necropsy[*3] 27: Death, 1/3 animals; premature necropsy (males), 2/3 animals; premature necropsy (females), 3/3 animals. Loose/mucous/watery stool; red substance in feces; abnormal gait; vomiting; salivation; coarse fur; decreased activity; decreased body weight/food consumption; increased red blood cell count/hemoglobin/hematocrit; increased monocyte count/large unstained cell count; decreased reticulocyte count; increased APTT; decreased blood ALP/urea nitrogen/creatinine/total protein/globulin/total cholesterol/inorganic phosphorus; decreased blood sodium/chloride; increased urinary protein; increased kidney weight; increased bone resorption of the femur; osteochondral dysplasia of the sternum/alveolar bone; increased bone resorption of the alveolar bone; increased gastric mucus secretion; vacuolation of gastric parietal cells; calcareous deposits in the heart; fibrinoid necrosis of the cystic artery; calcareous deposits in the lingual artery; atrophy of the stratified epithelium of the tongue; calcareous deposits in the sublingual gland; atrophy of the epithelium of the cornea; atrophy of the mucosal epithelium of the gingiva; atrophy of the mucosal epithelium of the esophagus; atrophy of the acini of the salivary gland; degeneration/necrosis of the mucosal epithelium of the small/large intestine; erosion of the large intestine; vacuolation of the epithelium of the pancreatic duct (males and females); lateral position[*4]; blackish green substance in feces; nail peeling; decreased white blood cell count[*4]/neutrophil count[*4]/lymphocyte count[*4]; increased blood AST[*4]/total bilirubin[*4]/triglycerides[*4]; decreased blood albumin; increased urinary bilirubin; cardiac prominence; dark red site in the lung[*4]; dark red foci in the stomach; dark red discoloration[*4]/dark red content of the large intestine; dilatation of the common bile duct; increased bone resorption of the sternum; fibrinoid necrosis of the gastric artery; calcareous deposits in the aorta; fibrinoid necrosis of the liver/vesical artery[*4]; hemorrhage of the kidney; vacuolation of the epithelium of renal tubules[*4]; hemorrhage of the spleen/lung[*4]; calcareous deposits in the lung; atrophy of the epidermis[*4]; atrophy of the acini of the lacrimal gland[*4]; vacuolation of the	<1.5	4.2.3.2.5

Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
				epithelium of epididymis (males); decreased urinary pH; increased platelet count; dark red discoloration of the large intestine; gallbladder dilatation; osteochondral dysplasia of the femur; fibrinoid necrosis of the hepatic artery; vacuolation of the epithelium of renal tubules; atrophy of the epidermis; atrophy of the acini of lacrimal gland; atrophy of the mammary gland (females). Surviving animals ≥1.5: Increased gastric mucus secretion (males and females); osteochondral dysplasia of the femur (males). 5.4: Loose/mucous/watery stool; nail peeling/hemorrhage; long/coarse fur in the head and paws; decreased body weight/food consumption; decreased reticulocyte count; increased blood inorganic phosphorus; increased bone resorption of the femur; osteochondral dysplasia of the sternum/alveolar bone; increased bone resorption of the alveolar bone; calcareous deposits in the heart; atrophy of the stratified epithelium of the tongue; atrophy of the epithelium of the cornea; atrophy of the mucosal epithelium of the gingiva/esophagus; atrophy of the stratified epithelium of paw pads; atrophy of the acini of the salivary gland/lacrimal gland (males and females); decreased red blood cell count/hemoglobin/hematocrit; dark red site on the surface of the left ventricular myocardium of the heart; nail loss; increased bone resorption of the sternum; hemorrhage of the heart; calcareous deposits in the aorta; fibrinoid necrosis of the vesical artery (males); dark red site in the lung; fibrinoid necrosis of the hepatic artery; atrophy of the mammary gland; degeneration/necrosis of the mucosal epithelium of the small intestine (females).		
				After the end of the recovery period[*2] ≥5.4: Long fur; osteochondral dysplasia of the alveolar bone; calcareous deposits in the aorta (males and females); osteochondral dysplasia of the sternum (females). 27: Calcareous deposits in the heart (males and females); osteochondral dysplasia of the sternum (males). 5.4: Osteochondral dysplasia of the femur (males).		
Male and female dogs (beagle)	p.o.	13 weeks	0[*1], 0.5, 1, 2	≥1: Increased inorganic phosphorus (males and females). 2: Long/rough fur; atrophy of the stratified epithelium of the nail bed/tongue (males and females); atrophy of the epithelium of the cornea (females).	0.5	4.2.3.2.6

*1, 0.1 mol/L HCl; *2, only irreversible findings; *3, all animals were subjected to necropsy due to worsening of clinical signs on Day 14; *4, findings observed only in moribund animals.

5.3 Genotoxicity

Bacterial reverse mutation assay (Ames test), chromosomal aberration assay in human lymphoblast TK6 cells, and micronucleus assay in rats were conducted (Table 14). Tasurgratinib was not genotoxic.

Table 14. Genotoxicity studies

Type of study		Test system	Metabolic activation (Duration)	Concentration or dose	Result	Attached data CTD
In vitro	Ames	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2uvrA	S9−	0[*1], 2.29, 6.86, 20.6, 61.7, 185, 556[*2] μg/plate	Negative	4.2.3.3.1.1
			S9+	0[*1], 2.29, 6.86, 20.6, 61.7, 185, 556[*2], 1,667*[2] μg/plate	Negative	
	Chromosomal aberration	Human lymphoblast TK6 cells	S9− (4 hours)	0[*1], 9, 10, 11 μg/mL	Negative	4.2.3.3.1.2
			S9+ (4 hours)	0[*1], 30, 35, 40 μg/mL	Negative	
			S9− (24 hours)	0[*1], 4, 5, 7 μg/mL	Negative	
In vivo	Micronucleus	Male rats (Sprague Dawley) 2 days, p.o. gavage, peripheral blood		0[*3], 30, 100, 300, 600 mg/kg	Negative	4.2.3.3.2.1

*1, DMSO; *2, only for TA98; *3, 0.1 mol/L HCl.

5.4 Carcinogenicity

Since tasurgratinib is an antineoplastic agent intended to treat patients with advanced cancer, no carcinogenicity studies were conducted.

5.5 Reproductive and developmental toxicity

An embryo-fetal development study in rats was conducted (Table 15). The main toxicity findings observed were increased post-implantation resorption rate; external, skeletal, and visceral malformations; and skeletal anomalies.

The applicant's explanation based on the above study results:

Precautions concerning the following points will be provided appropriately to healthcare professionals through the package insert and other materials: (a) Women of childbearing potential and men should be instructed to use appropriate contraception during treatment with tasurgratinib and for 6 days after the end of treatment[30]; (b) the use of tasurgratinib in pregnant women or women who may possibly be pregnant is allowed only if the expected therapeutic benefits outweigh the possible risks; and (c) mothers receiving tasurgratinib should avoid breastfeeding because tasurgratinib may be transferred into human breast milk [see Section 4.4.2].

[30] This period was selected based on the duration corresponding to 5 times the half-life of tasurgratinib administered at the proposed dosage and administration (half-life, 11.9-22.7 hours for tasurgratinib and 12.1-28.0 hours for M2; duration, 28 × 5 = 140 hours) according to "Guidance on the Need for Contraception Related to Use of Pharmaceuticals" (PSEHB/PED Notification No. 0216-1 by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, and PSEHB/PSD Notification No. 0216-1 by the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated February 16, 2023).

Table 15. Reproductive and developmental toxicity study

Type of study	Test system	Route of administration	Administration period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached data CTD
Embryo-fetal development	Female rats (Sprague Dawley)	p.o.	Gestation Days 7-17 (once daily) Caesarean section: Gestation Day 20	0[*1], 0.6, 2, 5	Maternal animals None Embryos/fetuses ≥2: Retroesophageal subclavian artery.[*2] 5: Decreased body weight; increased post-implantation resorptions; unilateral hypoplasia of limbs[*2]; missing fingers[*2]; blunted or shortened tail tip[*2]; dilated lateral ventricles[*2]; small thymus[*2]; ventricular septum defect[*2]; right-sided aortic arch[*2]; absent kidney[*2]/renal pelvic dilatation[*2]; absent rib[*2]; short rib[*2]; absent thoracic vertebral arch[*2]; increased lumbar vertebrae[*3]; increased incidence of splitting of thoracic vertebrae[*3]/dumbbell-shaped ossification[*3]; decreased ossified sacral/caudal vertebrae.[*3]	Maternal animals (general toxicity): - Embryos/fetuses: -	4.2.3.5.2.1

*1: 0.1 mol/L HCl. *2: malformation. *3: variation.

5.6 Other toxicity studies

5.6.1 Photosafety

Tasurgratinib showed the ultraviolet absorption maximum at wavelengths of 290 to 700 nm and absorbed radiation in the ultraviolet-B (UVB) region, with a molar absorbance coefficient of 14,600 L/mol·cm at the maximum absorbance in the above wavelength range. In view of this, a phototoxicity study using mouse fibroblast cells was conducted (Table 16). Since there were no findings suggesting phototoxicity, the applicant explained that concerns about phototoxicity of tasurgratinib are unlikely to arise.

Table 16. Photosafety study

Type of study	Test system	Test method	Results	Attached data CTD
In vitro	Mouse fibroblast cells (BALB/c 3T3)	0,* 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, and 100 μg/mL UVA (5 J/cm^2) was irradiated.	PIF: 0.787, MPE: 0.007 No phototoxicity	4.2.3.7.7.1

*: DMSO

5.6.2 Safety evaluation of impurities

The potential mutagenicity of impurities (Impurity A, Impurity B, and Impurity C[31)]) detected at a level greater than the identification threshold specified in the ICH Q3A and Q3B guidelines was evaluated using a (Q) SAR model. These impurities were found to be non-mutagenic. The 13-week repeated-dose toxicity studies in rats (CTD 4.2.3.2.3) and dogs (CTD 4.2.3.2.5), as well as the micronucleus assay in rats (CTD 4.2.3.3.2.1), were conducted using the drug substance containing the above impurities. Under conditions exceeding the exposure to the impurities contained in tasurgratinib administered at the approved dosage and administration, no toxicity findings considered due to the impurities were observed.

31) An impurity with the same structure as that of the metabolite M2.

5.R Outline of the review conducted by PMDA

On the basis of the data submitted and the review presented in the sections below, PMDA has concluded that the applicant's explanation about the toxicity of tasurgratinib is acceptable.

5.R.1 Ectopic mineralization and bone/cartilage dysplasia

The applicant's explanation about ectopic mineralization and bone/cartilage dysplasia in organs and tissues of the whole body related to increased blood inorganic phosphorus and abnormal electrolyte parameters observed in rats and dogs at doses corresponding to exposure below the human exposure,[29)] and safety in humans related to these toxicity findings:

FGF23, a ligand of FGFR, regulates the balance of inorganic phosphorus and calcium in blood by inhibiting the resorption of phosphorus (*Mol Endocrinol*. 2010;24:2050-2064, *Cytokine Growth Factor Rev*. 2012;23:37-46, etc.). Therefore, the above toxicity findings are considered to be attributable to increased blood inorganic phosphorus due to FGFR inhibition by tasurgratinib. Adverse events related to ectopic mineralization and bone/cartilage dysplasia reported in clinical studies of tasurgratinib included hyperphosphatemia and arthralgia [see Section 7.2.2]. Hyperphosphatemia, if it persists, may lead to ectopic mineralization and other problems, but it is reversible and can be managed by treatment interruption/dose reduction of tasurgratinib. In view of this, dose adjustment criteria for hyperphosphatemia management will be specified in the package insert, and safety measures such as the provision of precautions about the management method will be taken. With these measures taken, tasurgratinib is unlikely to cause any safety problems in clinical settings.

PMDA's view:

PMDA accepted the applicant's explanation. Safety in humans related to the above toxicity findings is discussed in Section "7.R.3.3 Hyperphosphatemia" in view of the incidences of hyperphosphatemia and related conditions in clinical studies.

5.R.2 Other systemic toxicities

The applicant's explanation about safety in humans related to atrophy/opacity of the corneal epithelium, atrophic lesions in epithelial tissues of the whole body, and mucosal degeneration/necrosis of the stomach/small intestine/large intestine, as well as fibrinoid necrosis and focal hemorrhage in arterioles, observed in rats and dogs at doses corresponding to exposure below the human exposure[29)]:

In view of the points described below, all the above toxicity findings are considered to be associated with FGFR inhibition by tasurgratinib. Although eye disorders [see Section 7.R.3.5], nail disorders [see Section 7.R.3.6], skin disorders [see Section 7.R.3.7], gastrointestinal disorders [see Section 7.R.3.8, 3], and hemorrhage [see Section 7.R.3.8, 4] were reported as related adverse events in clinical studies, these events could be managed by taking appropriate measures such as treatment interruption and dose reduction and are therefore considered to be tolerable.

- Inhibition of FGFR2 may induce atrophic changes in epithelial tissues (*Science*. 1994;266:819-822).
- Cell activation signals of FGF are involved in the cell proliferation/regeneration of the epithelium, maintenance of progenitor cells, differentiation of mucus-secreting cells, and other activities in the stomach/intestines (*Int J Oncol*. 2006;29:163-168, *Prog Mol Biol Transl Sci*. 2010;96:93-115, *Dev Biol*.

2007 1;303:295-310), and inhibition of FGFR may adversely affect the proliferation/differentiation of the gastrointestinal mucosa.

- FGF, like VEGF, promotes angiogenesis (*Trends Pharmacol Sci*. 2001;22:201-207), and inhibition of FGFR may adversely affect vascular cells.

PMDA's view:

PMDA accepted the applicant's explanation. Effects on the cornea, epithelial tissues, gastrointestinal tract, and vascular system in humans are discussed in Sections "7.R.3.5 Eye disorders (except for retinal disorder)," "7.R.3.6 Nail disorders," "7.R.3.7 Skin disorders (except for nail disorders)," "7.R.3.8, 3 Gastrointestinal disorders," and "7.R.3.8, 4 Hemorrhage" in view of the incidences of related adverse events in clinical studies.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Tasurgratinib comes in [redacted] and tablets for [redacted]. The PK and other parameters of tasurgratinib were investigated using these formulations (Table 17). The proposed commercial formulation is 35 mg tablets ([redacted]).

Table 17. Formulations used in clinical studies

Formulation	Study
[redacted] containing ^{14}C-labeled tasurgratinib	Foreign phase I study (Study 002)
([redacted] mg)	Japanese phase I study (Study 101)
([redacted] mg)	Japanese phase I study (Study 101)
Tablets ([redacted]) (35 mg)	Japanese phase I study (Study 003), global phase II study (Study 201)

(a) Tasurgratinib and (b) M2 (dealkylated form) levels in human plasma were determined by LC-MS/MS (lower limit of quantification: (a) 0.0250, 0.250 or 1.00 ng/mL,[32)] and (b) 0.0250 or 0.500 ng/mL[33)], respectively).

6.1.1 Japanese study

6.1.1.1 Part A of the Japanese phase I study (CTD 5.3.3.4.1: Study 003 [October 2020 to March 2021])

A 2-group, 2-period crossover study[34)] was conducted to investigate the effect of food on the PK of tasurgratinib and M2 in 14 healthy adults (14 subjects included in the PK analysis). Subjects received a single oral dose of tasurgratinib 35 mg in the fasted state[35)] or 30 minutes after a high-fat meal[36)] in the 2 administration periods, separated by a 5-day washout period.

32) In (a) Study 002, (b) Study 003, (c) Study 101, and (d) Study 201, the lower limit of quantification of the measurement method used was (a) 0.250 ng/mL, (b) 0.0250 ng/mL, (c) 0.250 and 1.00 ng/mL, and (d) 0.250 ng/mL, respectively.
33) The lower limit of quantification of the measurement method used was 0.500 ng/mL (Studies 002, 101, and 201) and 0.0250 ng/mL (Study 003).
34) At the time of planning, the study was designed to investigate the effect of a low-fat meal on the PK of tasurgratinib and M2. However, since the point estimates of the ratios of the geometric means of C_{max} and AUC after a high-fat meal to those in the fasted state did not meet the predetermined criteria (<0.5 or >2.0), the effect of a low-fat meal was not investigated.
35) Administered after ≥10-hour fasting, followed by 4-hour fasting.
36) A total of 800 to 1,000 kcal, of which 50% was from fat.

The ratios of the geometric means [90% confidence interval (CI)] of C_{max} and AUC_{inf} of (a) tasurgratinib and (b) M2 after the high-fat meal to those in the fasted state were (a) 0.672 [0.567, 0.797] and 0.771 [0.699, 0.851], and (b) 0.532 [0.467, 0.606] and 0.702 [0.646, 0.763], respectively.

6.1.1.2 Part B of the Japanese phase I study (CTD 5.3.3.4.1: Study 003 [October 2020 to March 2021])

An open-label, uncontrolled study was conducted to investigate the effect of a proton pump inhibitor (rabeprazole) on the PK of tasurgratinib and M2 in 14 healthy adults (14 subjects included in the PK analysis). Subjects received a single oral dose of tasurgratinib 35 mg on Days 1 and 11, and rabeprazole 20 mg orally QD from Days 7 to 11.

The ratios of the geometric means [90% CI] of C_{max} and AUC_{inf} of (a) tasurgratinib and (b) M2 following coadministration of tasurgratinib with rabeprazole to those following administration of tasurgratinib alone were (a) 1.07 [0.917, 1.25] and 1.08 [0.995, 1.17], respectively, and (b) 1.09 [0.964, 1.24] and 1.18 [1.10, 1.27], respectively.

On the basis of the above, coadministration of tasurgratinib with the proton pump inhibitor did not clearly affect the PK of tasurgratinib or M2. The applicant therefore considers that there is no need to provide precautions regarding the coadministration of tasurgratinib with drugs that affect the gastric PH, such as proton pump inhibitors

6.2 Clinical pharmacology

6.2.1 Japanese studies

6.2.1.1 Japanese phase I study (CTD 5.3.5.2.1: Study 101 [October 2014 to September 2021])

An open-label, uncontrolled study was conducted to investigate the PK and other parameters of tasurgratinib in 24 patients with advanced solid cancers (24 subjects included in the PK analysis). Subjects received a single oral dose of tasurgratinib 1 to 180 mg in the fasted state[37] on Day 1, followed by the same oral dose QD in the fasted state[38] starting between Day 8 and Day 10. This study investigated the plasma concentrations[39] of tasurgratinib and M2.

Table 18 shows the PK parameters of tasurgratinib and M2. Following administration of tasurgratinib at 1 mg and 2 mg, plasma concentrations of tasurgratinib and M2 were below the lower limit of quantification in all subjects except for 1 subject.[40] The accumulation ratios[41] of tasurgratinib and M2 following oral QD administration of tasurgratinib 16 to 180 mg ranged from 1.17 to 2.28 and 1.19 to 2.35, respectively, showing that the accumulation ratios tended to increase with escalating doses of tasurgratinib ≥140 mg (accumulation

[37] Administered after ≥10-hour fasting, followed by 2-hour fasting.
[38] On Day 1 of multiple-dose administration, tasurgratinib was administered after ≥10-hour fasting, followed by 2-hour fasting. On subsequent days, tasurgratinib was administered ≥2 hours after breakfast, followed by 1-hour fasting after administration.
[39] The plasma M2 concentration was investigated at doses of ≥4 mg.
[40] C_{max} after multiple doses of tasurgratinib 1 mg for 8 days was 1.65 ng/mL.
[41] Ratio of AUC_{24h} on Day 8 of multiple dosing to that after single-dose administration (Day 1).

ratios of tasurgratinib and M2 following oral QD administration of tasurgratinib ≥140 mg were ≥1.97 and ≥2.12, respectively).

Table 18. PK parameters of tasurgratinib and M2

Dose (mg)	Measurement day	Analyte	N	C_{max} (ng/mL)	t_{max}*2 (h)	AUC_{24h} (ng·h/mL)	$t_{1/2}$ (h)	M/P ratio*3 (%)
4	Day 1	Tasurgratinib	2	0.67, 2.41	1.00, 2.02	5.71*4	1.84*4	-
		M2	2	1.47, 2.68	1.98, 5.02	-	-	-
	Day 8*1	Tasurgratinib	2	0.98, 1.29	0.98, 1.00	-	-	-
		M2	2	1.52, 2.19	0.98, 3.02	-	-	-
8	Day 1	Tasurgratinib	2	2.80, 2.98	2.92, 3.00	19.8*4	-	-
		M2	2	1.47, 1.97	2.92, 5.00	-	-	-
	Day 8*1	Tasurgratinib	2	2.58, 7.97	0.98, 2.08	34.4, 60.6	-	-
		M2	2	2.32, 10.3	1.97, 3.12	34.3, 69.6	-	108, 124
16	Day 1	Tasurgratinib	2	5.03, 14.5	1.02, 3.00	40.6, 74.7	6.91, 16.9	-
		M2	2	4.20, 20.6	3.00, 3.05	43.0, 147	7.62, 16.6	119, 222
	Day 8*1	Tasurgratinib	2	8.50, 25.6	1.00, 1.03	48.2, 199	-	-
		M2	2	5.29, 28.5	1.97, 2.07	42.7, 299	-	95.8, 162
30	Day 1	Tasurgratinib	2	13.4, 42.8	0.93, 5.15	125, 214	21.2, 24.1	-
		M2	2	10.1, 28.3	2.02, 5.15	141, 238	20.7, 22.3	132, 138
	Day 8*1	Tasurgratinib	2	9.67, 17.0	3.00, 4.97	106, 230	-	-
		M2	2	11.0, 13.8	1.97, 5.00	129, 258	-	121, 132
60	Day 1	Tasurgratinib	3	38.7 ± 4.69	3.00 (2.97, 4.98)	352 ± 111	21.0 ± 5.50	-
		M2	3	35.1 ± 19.1	4.98 (3.00, 5.07)	397 ± 203	23.1 ± 5.66	138 ± 74.0
	Day 8*1	Tasurgratinib	1	39.4	3.00	422	-	-
		M2	1	53.3	3.00	704	-	180
100	Day 1	Tasurgratinib	3	85.9 ± 30.8	4.95 (2.97, 5.10)	851 ± 394	15.2 ± 1.84	-
		M2	3	38.4 ± 4.36	4.95 (2.97, 5.10)	463 ± 107	20.0 ± 0.794	73.3 ± 22.1
	Day 8*1	Tasurgratinib	3	116 ± 3.79	2.97 (2.03, 5.00)	1,380 ± 471	-	-
		M2	3	55.4 ± 14.5	5.00 (4.98, 5.05)	805 ± 195	-	67.5 ± 23.8
140	Day 1	Tasurgratinib	3	227 ± 118	4.88 (3.00, 5.08)	2,460 ± 1,580	18.3 ± 5.13	-
		M2	3	63.8 ± 36.1	5.00 (4.88, 5.08)	741 ± 290	26.0 ± 8.52	65.2 ± 63.1
	Day 8*1	Tasurgratinib	3	372 ± 173	5.00 (2.98, 5.08)	4,800 ± 3,480	-	-
		M2	3	106 ± 51.8	5.00 (2.98, 5.08)	1,620 ± 460	-	51.1 ± 39.2
180	Day 1	Tasurgratinib	2	110, 177	1.95, 5.00	1,260, 2,470	15.2, 27.1	-
		M2	2	26.8, 62.7	5.00, 5.02	361, 1,040	24.7, 31.2	37.3, 60.6
	Day 8*1	Tasurgratinib	3	337 ± 60.3	5.00 (3.05, 5.08)	3,940 ± 775	-	-
		M2	3	98.0 ± 39.5	5.00 (3.05, 5.08)	1,500 ± 686	-	39.5 ± 12.5

Mean ± standard deviation (individual data when n = 1 or 2); -, not calculated; *1, Day 8 of multiple dosing, *2, median (minimum, maximum); *3, M2-to-tasurgratinib exposure ratio calculated based on AUC_{inf}; *4, 1 subject.

Tasurgratinib exposure showed a more than dose-proportional increase, and the M2-to-tasurgratinib exposure ratio tended to decrease with increasing dose. The applicant explained that, while this trend may be attributable to the saturation of CYP4F12-mediated metabolism of tasurgratinib with increasing dose, the PK of tasurgratinib is considered to be generally linear in view of the fact that the tasurgratinib dose was not selected as a significant covariate for CL/F in the population pharmacokinetic (PPK) analysis [see Section 6.2.6].

6.2.2 Foreign studies

6.2.2.1 Foreign phase I study (CTD 5.3.3.1.1: Study 002 [September to October 2020])

An open-label, uncontrolled study was conducted to investigate the mass balance of tasurgratinib in 8 healthy adults (8 subjects included in the PK analysis). A single oral dose of ^{14}C-labeled tasurgratinib 35 mg was administered to investigate radioactivity concentrations in plasma, urine, and feces.

Up to 48 hours post-dose, unchanged tasurgratinib, M2, and M9[42)] (oxidized derivative of M2) were mainly detected in plasma (accounting for 30.9%, 20.6%, and 12.3%, respectively, of the total radioactivity in plasma).

The urinary and fecal excretion rates of radioactivity relative to the administered radioactivity up to 672 hours post-dose were 5.84% and 79.7%, respectively. The urinary and fecal excretion rates of unchanged tasurgratinib relative to the administered radioactivity up to 672 hours post-dose were 2.05% and 32.08%, respectively. In urine and feces, M2 was detected as a major metabolite (the excretion relative to the administered radioactivity was 2.55% and 30.53%, respectively).

6.2.3 Drug interaction study (CTD 5.3.3.4.1: Study 003 [October 2020 to March 2021])

A clinical study was conducted to investigate pharmacokinetic interactions following concomitant use of tasurgratinib with rifampicin (strong CYP3A inducer) (Table 19).

Table 19. Effect of concomitant drugs on the PK of tasurgratinib and M2 (assessment of tasurgratinib as a victim drug in drug-drug interaction)

Study identifier	Dosage regimen of tasurgratinib	Concomitant drug	Dosage regimen of the concomitant drug	Number of subjects (With/without concomitant drug)	Analyte	Ratio of geometric mean [90% CI] (With/without concomitant use)	
						C_{max}	AUC_{inf}
Part C of Study 003	35 mg QD p.o. on Days 1 and 13	Rifampicin	600 mg QD p.o. from Days 7 to 18	14/14	Tasurgratinib	1.02 [0.873, 1.19]	0.841 [0.739, 0.958]
					M2	1.25 [1.05, 1.49]	0.878 [0.757, 1.02]

The applicant's explanation based on the above results:

- Concomitant use of tasurgratinib with CYP3A inducers is unlikely to reduce exposure to tasurgratinib and M2. Therefore, it is considered unnecessary to provide precautions regarding the concomitant use of tasurgratinib with CYP3A inducers.
- The above study results suggest that CYP3A contributes marginally to the metabolism of tasurgratinib. Therefore, it is considered unnecessary to provide precautions regarding the concomitant use of tasurgratinib with CYP3A inhibitors.

6.2.4 Use of tasurgratinib in patients with renal impairment

No clinical studies have been conducted in patients with renal impairment to investigate the effect of renal impairment on the PK of tasurgratinib.

In view of the following points, the applicant explained that dose adjustment of tasurgratinib is not necessary for patients with renal impairment.

- The results of the foreign phase I study (Study 002) suggest that renal excretion contributes marginally to the elimination of tasurgratinib [see Section 6.2.2.1].
- As a result of the PPK analysis, eGFR was not selected as a significant covariate for the CL/F of

[42)] (*R*)-M9 and (*S*)-M9.

tasurgratinib or M2 [see Section 6.2.6].

- In the Japanese phase I study (Study 101) and the global phase II study (Study 201), the incidences of (a) adverse events leading to death, (b) serious adverse events, (c) adverse events leading to treatment discontinuation of tasurgratinib, (d) adverse events leading to treatment interruption of tasurgratinib, and (e) adverse events leading to dose reduction of tasurgratinib in patients with normal renal function[43] (38 subjects), patients with mild renal impairment (30 subjects), and patients with moderate renal impairment (14 subjects) were (a) 2.6%, 3.3%, and 14.3%, respectively, (b) 31.6%, 30.0%, and 42.9%, respectively, (c) 5.3%, 6.7%, and 21.4%, respectively, (d) 42.1%, 56.7%, and 50.0%, respectively, and (e) 50.0%, 53.3%, and 50.0%, respectively. The incidences of adverse events leading to death, serious adverse events, and other adverse events tended to increase in patients with moderate renal impairment, compared to patients with normal renal function. However, the incidence of adverse events for which a causal relationship to tasurgratinib could not be ruled out did not tend to increase.[44] Given the above finding, the differences in the incidence of adverse events were not attributable to the severity of renal impairment, and the proposed dosage and administration of tasurgratinib is therefore tolerable even in patients with renal impairment.

6.2.5 Relationship between exposure and QT/QTc interval changes

The relationship between the plasma tasurgratinib concentrations and changes in the Fridericia-corrected QT interval from baseline (ΔQTcF) was investigated using a linear mixed-effects model based on data from the global phase II study (Study 201). The ΔQTcF [90% CI] at the geometric mean C_{max} (112.6 ng/mL) of tasurgratinib at steady state (Day 8) was predicted to be 8.49 [4.63, 12.35] ms.

The applicant explained that although the upper limit of 90% CI for the predicted ΔQTcF was slightly greater than 10 ms, tasurgratinib administered at the proposed dosage and administration is unlikely to prolong the QT/QTc interval in view of the incidences of adverse events related to electrocardiogram abnormalities in clinical studies [see Sections 7.2.1 and 7.2.2].

6.2.6 PPK analysis

A PPK analysis was performed using a non-linear mixed-effects model (software, NONMEM Version 7.5 or later) based on the PK data of tasurgratinib (1,154 plasma concentration data from 93 subjects) and M2 (1,150 plasma concentration data from 93 subjects)[45] obtained in the Japanese phase I study (Study 101) and the global phase II study (Study 201). The PK of tasurgratinib was described using a 2-compartment model with

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[43] Renal function was classified according to the following criteria: normal, CrCL ≥90 mL/min; mild impairment, CrCL ≥60 and <90 mL/min; moderate impairment, CrCL ≥30 and <60 mL/min.

[44] The incidences of (a) adverse events leading to death and (b) serious adverse events for which a causal relationship to tasurgratinib could not be ruled out in patients with normal renal function, patients with mild renal impairment, and patients with moderate renal impairment were (a) 0% for all, and (b) 7.9%, 6.7%, and 7.1%, respectively.

[45] Baseline characteristics (median [minimum, maximum]) of the patients included in the analysis or the number of patients in each category of the analysis are as follows:
Body weight, 60 (40, 99) kg; sex, 49 males and 44 females; age, 58 (33, 80) years; race, 57 Japanese patients and 36 Chinese patients; AST, 28 (11, 149) IU/L; ALT, 19 (5, 106) IU/L; total bilirubin, 10.3 (3.4, 27.8) μmol/L; albumin, 40.0 (25.0, 50.7) g/L; eGFR, 95 (51, 206) mL/min/1.73 m^2; cancer type, 14 patients with solid cancers (patients with solid cancers enrolled in the dose escalation part of Study 101), 69 patients with cholangiocarcinoma, and 10 patients with gastric cancer; ECOG PS, 48 patients with Score 0 and 45 patients with Score 1; and use of concomitant gastric secretion inhibitors, 32 patients with use and 61 patients without use.

zero- and first-order absorption processes and a linear elimination process. The PK of M2 was described using a 2-compartment model with zero- and first-order formation processes with lag time and a linear elimination.

In this analysis, possible covariates of tasurgratinib and M2 for (a) CL/F and (b) V_2/F and V_3/F were (a) age, body weight, AST, ALT, total bilirubin, albumin, eGFR, dose, age group (<65 years or ≥65 years), sex, race, cancer type, ECOG PS, and concomitant gastric secretion inhibitors, and (b) age, body weight, albumin, and sex. As a result of assessments, there were no significant covariates selected for the CL/F, V_2/F, or V_3/F of tasurgratinib. Cancer type was selected as a significant covariate for the CL/F of M2, and there were no significant covariates selected for V_2/F or V_3/F of M2.

6.2.7 Relationships between exposure and efficacy and safety

6.2.7.1 Relationship between exposure and efficacy

The relationships of exposure to tasurgratinib and M2[46)] (sum of the AUC_{ss} of tasurgratinib and M2) with both response rate and progression free survival (PFS) were investigated based on the results of the global phase II study (Study 201). No clear relationship was observed between exposure to tasurgratinib and M2 and the response rate or PFS.

6.2.7.2 Relationship between exposure and safety

The relationship between exposure to tasurgratinib or M2[46)] ($C_{max,ss}$ or AUC_{ss}) and adverse events[47)] was investigated based on the results of the Japanese phase I study (Study 101) and the global phase II study (Study 201). Exposure to tasurgratinib and M2 ($C_{max,ss}$ and AUC_{ss}) tended to be higher with higher grades of hyperphosphatemia. No clear relationship was observed between exposure to tasurgratinib and M2 and any of the other adverse events.

6.2.8 Differences in PK between Japanese and non-Japanese patients

According to the applicant, there are no clear differences in the PK of tasurgratinib or M2 between Japanese and non-Japanese patients in view of the following points:

- In the global phase II study (Study 201), no clear differences were observed in the C_{trough} of tasurgratinib or M2 between Japanese and non-Japanese patients at each time point in Cycles 1 to 3[48)] (Figure 2).

[46)] Estimated by the PPK analysis [see Section 6.2.6].
[47)] Hyperphosphataemia, palmar-plantar erythrodysaesthesia syndrome, diarrhoea, stomatitis, and paronychia.
[48)] Each cycle consisted of 28 days.

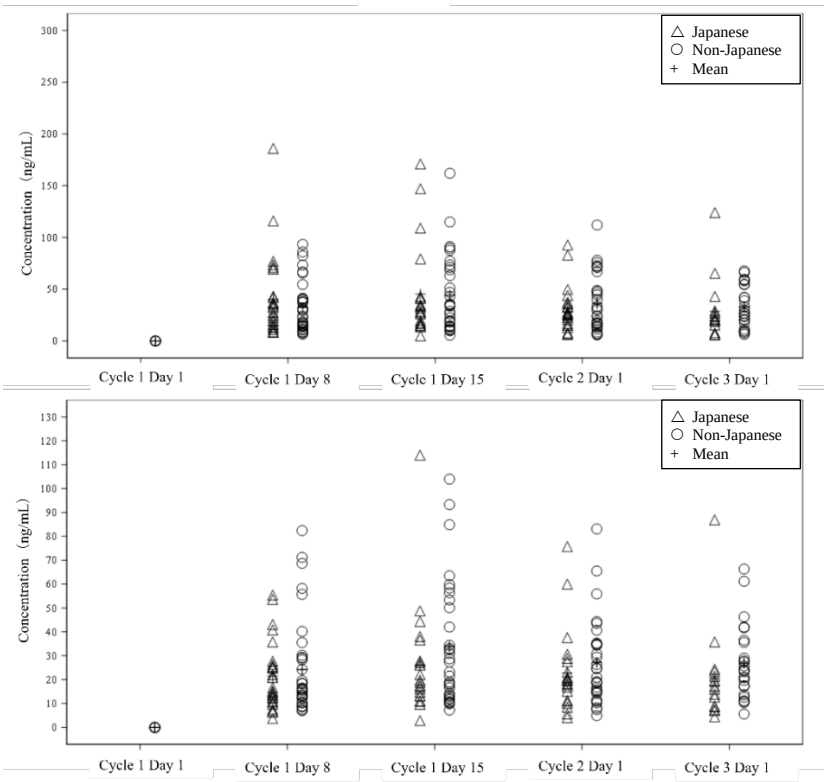

Figure 2. C_{trough} of tasurgratinib and M2
(Top, tasurgratinib; bottom, M2)

- Race was not selected as a significant covariate for the CL/F of tasurgratinib or M2 in the PPK analysis [see Section 6.2.6]. In addition, no clear differences were observed in the PK parameters of tasurgratinib or M2 at steady state following oral QD administration of tasurgratinib 140 mg in the fasted state between Japanese patients with cholangiocarcinoma in the Japanese phase I study (Study 101) and the global phase II study (Study 201) and non-Japanese patients with cholangiocarcinoma in the global phase II study (Study 201) (Table 20).

Table 20. PK parameters of tasurgratinib and M2 (estimates)

Analyte	Population	N	$C_{max,ss}$* (ng/mL)	AUC_{ss}* (ng·h/mL)
Tasurgratinib	Japanese	34	132 ± 97.1	1,710 ± 1,240
	Non-Japanese	35	129 ± 81.0	1,690 ± 962
M2	Japanese	34	71.4 ± 43.8	1,100 ± 712
	Non-Japanese	35	87.0 ± 62.2	1,370 ± 970

Mean ± standard deviation. *: The $C_{max,ss}$ and AUC_{ss} of M2 were estimated using unchanged tasurgratinib-equivalent concentrations calculated based on the molecular weight.

6.R Outline of the review conducted by PMDA

PMDA's view:

On the basis of the data submitted, the applicant's explanation about the clinical pharmacology of tasurgratinib is acceptable, except the review presented in the sections below.

6.R.1 Food effect

The applicant's explanation about the timing of tasurgratinib administration relative to meal intake:

The protocol of the global phase II study (Study 201) specified that tasurgratinib 140 mg should be administered orally QD in the fasted state (≥2-hour fasting before administration and ≥1-hour fasting after administration). This study demonstrated the clinical usefulness of tasurgratinib [see Sections 7.R.2 and 7.R.3]. The results of Part A of the Japanese phase I study (Study 003) showed that exposure to tasurgratinib and M2 decreased following administration after a high-fat meal, compared with that following administration in the fasted state [see Section 6.1.1.1]. Therefore, precautions should be provided in the "Precautions Concerning Dosage and Administration" section to ensure that administration of tasurgratinib should be avoided after a high-fat meal. However, it is considered unnecessary to specify the timing of tasurgratinib administration relative to meal intake, in view of the following points:

- No clear relationship was observed between exposure to tasurgratinib and M2 and efficacy [see Section 6.2.7.1].
- Although no clinical studies were conducted to investigate the effect of a low-fat meal on the PK of tasurgratinib and M2, the effect of a low-fat meal on the PK of tasurgratinib and M2 is considered to be small compared with that of a high-fat meal.

PMDA's view:

The clinical usefulness of tasurgratinib was demonstrated in the global phase II study (Study 201). The protocol of the study specified that tasurgratinib 140 mg should be administered orally QD in the fasted state (≥2-hour fasting before administration and ≥1-hour fasting after administration) [see Sections 7.R.2 and 7.R.3]. Tasurgratinib should be administered in the fasted state in view of the following points:

- The results of Part A of the Japanese phase I study (Study 003) showed that exposure to tasurgratinib and M2 decreased following administration after a high-fat meal, compared with that following administration in the fasted state.
- The relationship between exposure to tasurgratinib and M2 and efficacy [see Section 6.2.7.1] was investigated based on the data following oral QD administration of tasurgratinib 140 mg in the fasted state. Therefore, whether decreased exposure following oral QD administration of tasurgratinib 140 mg in the postprandial state affects the efficacy is unknown.
- Since there are no clinical study results investigating the effect of low-fat meals on the PK of tasurgratinib and M2, the extent of the effect is unknown.

The applicant is therefore required to specify that tasurgratinib should be administered in the fasted state in the Dosage and Administration section, and then provide precautions in the "Precautions Concerning Dosage and Administration" section to ensure that administration of tasurgratinib is avoided within 1 hour before and 2 hours after a meal [see Section 7.R.5.1].

6.R.2 Use of tasurgratinib in patients with hepatic impairment

No clinical studies have been conducted in patients with hepatic impairment to investigate the effect of hepatic impairment on the PK of tasurgratinib.

The applicant's explanation about the use of tasurgratinib in patients with hepatic impairment:

- In view of the following points, the applicant explained that dose adjustment of tasurgratinib is considered unnecessary for patients with mild hepatic impairment.
  - In the PPK analysis, AST, ALT, total bilirubin, and albumin were not selected as significant covariates for the CL/F of tasurgratinib or M2 [see Section 6.2.6].
  - In the Japanese phase I study (Study 101) and the global phase II study (Study 201), the incidences of (a) adverse events leading to death, (b) serious adverse events, (c) adverse events leading to treatment discontinuation of tasurgratinib, (d) adverse events leading to treatment interruption of tasurgratinib, and (e) adverse events leading to dose reduction of tasurgratinib in patients with normal hepatic function[49)] (52 subjects) and patients with mild hepatic impairment (30 subjects) were (a) 1.9% and 10.0%, respectively; (b) 23.1% and 50.0%, respectively; (c) 3.8% and 16.7%, respectively; (d) 42.3% and 60.0%, respectively; and (e) 61.5% and 33.3%, respectively. The incidences of the above adverse events tended to be higher in patients with mild hepatic impairment than in patients with normal hepatic function. However, given that the incidence of adverse events for which a causal relationship to tasurgratinib could not be ruled out did not tend to increase ((a) 0% for both and (b) 9.6% and 3.3%, respectively), the differences in the incidence of adverse events are unlikely to be attributable to the severity of hepatic impairment, and the proposed dosage and administration of tasurgratinib is therefore considered to be tolerable even in patients with mild hepatic impairment.
- No clinical studies were conducted in patients with moderate or severe hepatic impairment. However, since tasurgratinib is eliminated mainly by hepatic metabolism [see Section 6.2.2.1], the package insert should include a cautionary statement to the effect that tasurgratinib should be carefully administered to this patient population.

A clinical study in patients with mild or moderate hepatic impairment is ongoing to investigate the PK of tasurgratinib.

PMDA's view:

PMDA largely accepted the applicant's explanation. However, given that (a) tasurgratinib is eliminated mainly by hepatic metabolism and (b) only limited information is available on the safety of tasurgratinib in patients with hepatic impairment, including those with mild hepatic impairment, tasurgratinib should be carefully administered to patients with hepatic impairment regardless of its severity. The applicant should provide precautions regarding use in this patient population in the package insert. In addition, as soon as the results of the clinical study to investigate the PK of tasurgratinib in patients with mild or moderate hepatic impairment become available, the applicant should appropriately provide information to healthcare professionals.

[49)] Hepatic function was classified according to the following criteria: normal, both AST and total bilirubin ≤ upper limit of normal (ULN); mild impairment, total bilirubin between > ULN and (a) <1.5 times ULN or (b) AST > ULN.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from the studies shown in Table 21.

Table 21. List of clinical studies on efficacy and safety

Data category	Region	Study identifier	Phase	Population	Number of enrolled subjects	Outline of dosage regimen	Main endpoints
Evaluation	Japan	Study 101	I	Part 1 Patients with advanced solid cancers Part 2 Patients with gastric cancer or cholangiocarcinoma harboring *FGFR2* genetic abnormalities	Part 1 24 Part 2 16	Part 1 Administration of a single oral dose of tasurgratinib 1 to 180 mg in the fasted state, followed by the same oral dose QD in the fasted state starting between Day 8 to Day 10. Part 2 (1) Tasurgratinib 140 mg QD administered orally in the fasted state.	Tolerability Safety PK
		Study 003	I	Healthy adults	Part A 14 Part B 14 Part C 14	Part A Administration of a single oral dose of tasurgratinib 35 mg in the fasted state or after a high-fat meal. Part B Administration of a single oral dose of tasurgratinib 35 mg alone or concomitantly with rabeprazole in the fasted state. Part C Administration of single oral dose of tasurgratinib 35 mg alone or concomitantly with rifampicin in the fasted state.	PK
	Global	Study 201	II	Patients with unresectable cholangiocarcinoma with *FGFR2* gene fusion who had received prior chemotherapy	63	Tasurgratinib 140 mg QD administered orally in the fasted state.	Efficacy Safety
	Foreign	Study 002	I	Healthy adults	8	Administration of a single oral dose of ^{14}C-labeled tasurgratinib 35 mg in the fasted state.	PK

An outline of each clinical study is provided below. The data submitted for safety evaluation were complied, and the most common adverse events other than deaths observed in each clinical study are described in Section "7.2 Adverse events observed in clinical studies," and the results of PK studies are described in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Clinical pharmacology

The applicant submitted the results of 2 clinical pharmacology studies (Studies 002 and 003) [see Sections 6.1 and 6.2]. In these studies, no deaths were observed during the study treatment or within 28 days after the end of the treatment.

7.1.2 Japanese studies

7.1.2.1 Japanese phase I study (CTD 5.3.5.2.1: Study 101 [October 2014 to September 2021])

An open-label, uncontrolled study was conducted at 18 study sites in Japan to investigate the tolerability, safety and other parameters of tasurgratinib in patients with advanced solid cancers[50] (target sample size, 20 subjects in Part 1 and 10 subjects with gastric cancer and 5-10 subjects with cholangiocarcinoma in Part 2).

Subjects were treated at the dosage regimen as shown below. The study treatment was continued until the subject's disease progressed or the discontinuation criteria were met.

Part 1

- Subjects received a single oral dose of tasurgratinib 1, 2, 4, 8, 16, 30, 60, 100, 140, or 180 mg in the fasted state, followed by the same oral dose QD in the fasted state[51] starting between Day 8 and Day 10.

Part 2

- Subjects received tasurgratinib 140 mg QD orally in the fasted state.[51]

All 40 patients enrolled in this study (2 subjects each in the 1-30 mg groups and 3 subjects each in the 60-180 mg groups in Part 1, and 10 subjects with gastric cancer and 6 subjects with cholangiocarcinoma in Part 2) received tasurgratinib and were included in the safety analysis population. In Part 1, dose-limiting toxicities (DLTs) were evaluated in 20 subjects (2 subjects each in the 1-180 mg groups), excluding 4 subjects (1 subject each in the 60 mg, 100 mg, 140 mg, and 180 mg groups)[52] who discontinued the study during the DLT evaluation period.

In Part 1, DLT was evaluated during the period from the day of single-dose administration of tasurgratinib to 28 days after the start of continuous daily administration. In Part 1, the maximum tolerated dose (MTD) was not determined, but a dose of 140 mg QD was determined to be the recommended dose for Part 2 because DLTs were observed in 1 subject in the 180 mg group (Grade 3 AST increased and ALT increased). In Part 2, 140 mg QD was tolerable, and was therefore selected as the recommended Phase 2 dose (RP2D).

Concerning the safety, no deaths were observed during treatment with tasurgratinib or within 30 days after the end of the treatment.

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[50] Part 1 enrolled patients with advanced solid cancers, and Part 2 enrolled patients with gastric cancer harboring *FGFR2* gene amplification or high FGFR2 protein expression and patients with cholangiocarcinoma with *FGFR2* gene fusion.

[51] Fasted for ≥2 hours before administration and ≥1 hour after administration.

[52] No events meeting the definition of DLT were observed in these 4 subjects. The reason for study discontinuation was disease progression in 3 subjects and patient's request in 1 subject.

7.1.3 Global study

7.1.3.1 Global phase II study (CTD 5.3.5.2.2, Study 201 [January 2020 to ongoing (data cut-off on [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted at 56 study sites in Japan and China to investigate the efficacy and safety of tasurgratinib in patients with unresectable cholangiocarcinoma (intrahepatic or hilar cholangiocarcinoma) with *FGFR2* gene fusion[53)] who had received prior chemotherapy[54)] (target sample size, approximately 60 subjects[55)]).

Subjects received tasurgratinib 140 mg QD orally in the fasted state,[51)] and the study treatment was continued until the subject's disease progressed or the discontinuation criteria were met.

All 63 patients enrolled in this study received tasurgratinib and were included in the efficacy and safety analysis populations (of these, 28 patients were Japanese).

The primary endpoint of this study was the response rate, as assessed by the independent imaging review (IIR) committee based on the Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1, and the threshold response rate was set at 15%.[56)] Two interim analyses on efficacy were scheduled at the following time points: first when 40 subjects and second when 50 subjects underwent the evaluation at Cycle 6[57)] and the tumor assessment at Week 24, or discontinued the treatment before Cycle 6. If there were ≥15 responders[58)] at each time point, the study would be terminated early for efficacy. It was planned to perform the primary analysis at the time point when all subjects included in the efficacy analysis population underwent the evaluation at Cycle 6 and the tumor assessment at Week 24 or discontinued the treatment before Cycle 6.

For the efficacy data, Table 22 shows the results of the final analysis on the response rate as assessed by IIR based on RECIST ver.1.1, for the primary endpoint. The lower limit of 90% CI exceeded the pre-determined threshold response rate (15%) (data cut-off on [redacted], 20[redacted]).

53) Determined by the fluorescence *in situ* hybridization (FISH) method using tumor tissue specimens.
54) Patients who had received ≥1 chemotherapy regimen including gemcitabine.
55) Assuming the threshold value for the response rate, the primary endpoint, to be 15% (see Footnote 56) and the expected value to be 30% to 40%, with a 1-sided significance level of 5% and a sample size of 60 subjects, the power was estimated to be 84% to 99%. Therefore, the target sample size was set as 60 subjects.
56) The threshold was selected in reference to the report that the response rates with S-1 and gemcitabine were 6.9% to 7.5% in patients with unresectable biliary tract cancer who had received prior chemotherapy (*Invest New Drugs*. 2011;29:1066-1072, *Cancer Chemother Pharmacol*. 2013;71:1141-1146).
57) Each cycle consisted of 28 days.
58) This number was selected because the lower limit of 90% CI for the response rate would exceed the threshold if ≥15 of 60 to 64 subjects were responders at the time of the primary analysis. If then number of subjects included in the efficacy analysis exceeded 64, the first 64 subjects were to be included in the primary analysis.

Table 22. Best overall response and response rate
(assessed by IIR per RECIST ver.1.1, efficacy analysis population, data cut-off on [redacted], 20[redacted])

Best overall response	n (%)
	Overall population N = 63
CR	0
PR	19 (30.2)
SD	31 (49.2)
PD	12 (19.0)
NE	1 (1.6)
Response (CR + PR) (response rate [90% CI[*1]] [%])	19 (30.2 [20.7, 41.0][*2])

*1, Clopper-Pearson method; *2, 95% CI was [19.2, 43.0].

Concerning safety, deaths were observed in 6 of 63 subjects (9.5%) during treatment with tasurgratinib or within 30 days after the end of the treatment. The cause of death, except for deaths due to disease progression (4 subjects)[59] and unknown cause (1 subject), was myocardial ischemia in 1 subject, and a causal relationship of the event to tasurgratinib was ruled out. Four of these deaths involved Japanese patients, and the cause of death, except for deaths due to disease progression (2 subjects) and unknown cause (1 subject), was myocardial ischemia in 1 subject.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA's view:

Among the evaluation data submitted, the global phase II study (Study 201) in patients with unresectable cholangiocarcinoma with *FGFR2* gene fusion who had received prior chemotherapy is important for evaluating the efficacy and safety of tasurgratinib. The review is conducted mainly based on this study. The efficacy in Japanese patients is systematically evaluated based on the results of Study 201, in accordance with guidelines including the "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Amendment to 'Basic Principles on Global Clinical Trials (Reference Cases)' " (Administrative Notice dated December 10, 2021), and "Guidelines on General Principles for Planning and Design of Multi-Regional Clinical Trials" (PSEHB/PED Notification No. 0612-1 dated June 12, 2018).

7.R.2 Efficacy

As a result of the review presented below, PMDA has concluded that tasurgratinib showed a certain level of efficacy in patients with unresectable cholangiocarcinoma with *FGFR2* gene fusion who have received prior chemotherapy.

7.R.2.1 Efficacy endpoints and efficacy evaluation results

The applicant's explanation about the primary endpoint of Study 201 and the efficacy of tasurgratinib in patients with unresectable cholangiocarcinoma with *FGFR2* gene fusion who had received prior chemotherapy:

[59] The death in 1 subject who developed multiple organ dysfunction syndrome was considered to be associated with worsening of the primary disease, and the cause of death was determined to be disease progression.

If treatment response is achieved in patients with unresectable cholangiocarcinoma with *FGFR2* gene fusion who had received prior chemotherapy, the target patient population of Study 201, accompanying symptoms such as obstructive jaundice associated with tumor growth will improve. Achieving treatment response is clinically meaningful. Therefore, the response rate was selected as the primary endpoint of Study 201.

The response rate [90% CI] in the efficacy analysis population of Study 201 was 30.2% [20.7%, 41.0%], showing that the lower limit of 90% CI exceeded the threshold response rate of 15% [see Section 7.1.3.1]. Figure 3 shows the best percent changes in tumor diameter of the target lesions in the efficacy analysis population. The median duration [95% CI] of response[60] in 19 patients with confirmed response (complete response [CR] or partial response [PR]) was 5.6 [3.7, 9.3] months.

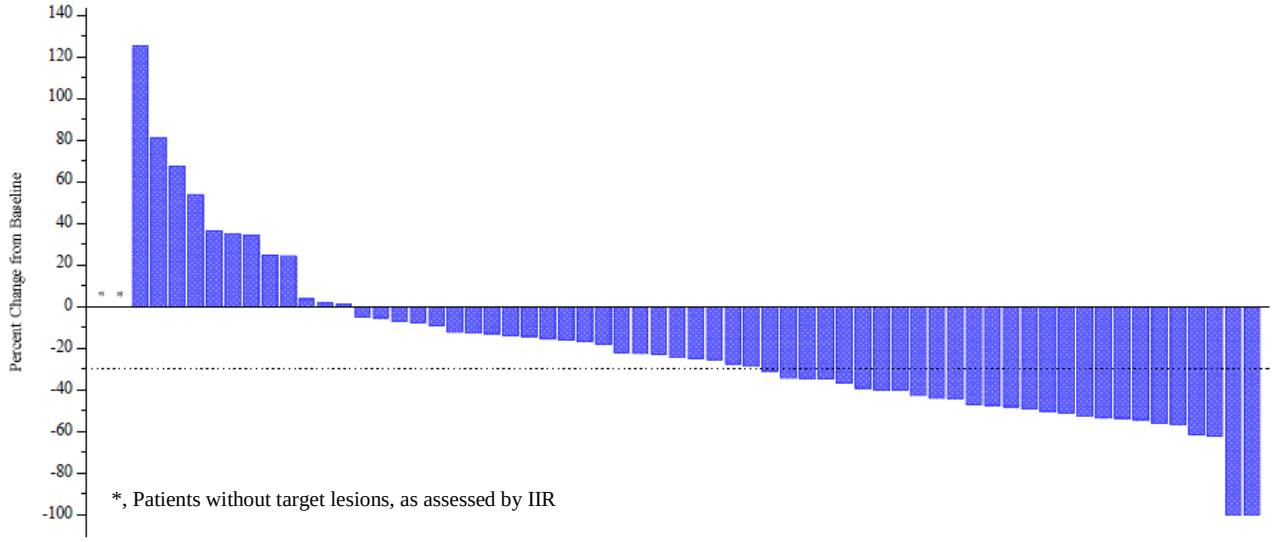

Figure 3. Best percent change in tumor diameter (target lesions)
(assessed by IIR per RECIST ver.1.1, efficacy analysis population, data cut-off on [redacted], 20[redacted])

The response rate with tasurgratinib obtained in Study 201 was clinically meaningful, and results in the Japanese population were consistent with those in the overall population (Table 23). Therefore, tasurgratinib is expected to have efficacy in the target patient population of Study 201.

Table 23. Best overall response and response rate in the Japanese population
(assessed by IIR per RECIST ver.1.1, efficacy analysis population, data cut-off on [redacted], 20[redacted])

Best overall response	n (%)
	Japanese population N = 28
CR	0
PR	7 (25.0)
SD	13 (46.4)
PD	8 (28.6)
NE	0
Response (CR + PR) (response rate [95% CI*] [%])	7 (25.0 [10.7, 44.9])

*: Clopper-Pearson method

[60] Defined as the time from the initial documentation of response (CR or PR) to the date of first documentation of progressive disease (PD) or death, in patients with confirmed response.

PMDA's view:
It is difficult to evaluate the survival benefits of tasurgratinib in patients with unresectable cholangiocarcinoma with *FGFR2* gene fusion who have received prior chemotherapy based on the results of the response rate, the primary endpoint of Study 201, because the relationship between overall survival (OS), a true endpoint, and the response rate in these patients remains unclear.

However, besides the above applicant's explanation about the efficacy of tasurgratinib, the *FGFR2* fusion gene is considered to be an oncogenic driver of tumor cell proliferation [see Section 3.R.1] and tasurgratinib is an FGFR inhibitor. Taken together, PMDA concluded that the results of Study 201 demonstrated a certain level of efficacy of tasurgratinib in patients with unresectable cholangiocarcinoma with *FGFR2* gene fusion who have received prior chemotherapy, including Japanese patients.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events observed in clinical studies"]

As a result of the review presented below, PMDA has concluded that adverse events requiring special attention during treatment with tasurgratinib are hyperphosphatemia, retinal detachment, eye disorders (except for retinal detachment), nail disorders, and palmar-plantar erythrodysesthesia syndrome.

PMDA has also concluded that although attention should be paid to the occurrence of the above adverse events during treatment with tasurgratinib, tasurgratinib is tolerable as long as physicians with adequate knowledge and experience in cancer chemotherapy take appropriate measures, such as monitoring and management of adverse events, and interruption and dose reduction of tasurgratinib.

7.R.3.1 Safety profile

The applicant's explanation about the safety profile of tasurgratinib based on the safety information obtained in Study 201:
Table 24 summarizes safety data from Study 201.

Table 24. Summary of safety (Study 201)

	n (%) N = 63
Any adverse event	63 (100)
Grade ≥3 adverse events	35 (55.6)
Adverse events leading to death	4 (6.3)
Serious adverse events	22 (34.9)
Adverse events leading to treatment discontinuation	6 (9.5)
Adverse events leading to treatment interruption	31 (49.2)
Adverse events leading to dose reduction	35 (55.6)

Table 25 shows the most common adverse events in Study 201. There were no adverse events leading to treatment discontinuation reported in ≥2% of subjects.

Table 25. Most common adverse events (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63
Any-grade adverse events[*1]	
Hyperphosphataemia	51 (81.0)
Palmar-plantar erythrodysaesthesia syndrome	28 (44.4)
Diarrhoea	23 (36.5)
Aspartate aminotransferase increased	20 (31.7)
Alanine aminotransferase increased	18 (28.6)
Stomatitis	16 (25.4)
Dry mouth	14 (22.2)
Pyrexia	14 (22.2)
Paronychia	14 (22.2)
Keratitis	13 (20.6)
Blood alkaline phosphatase increased	13 (20.6)
Blood creatinine increased	13 (20.6)
Lipase increased	13 (20.6)
Grade ≥3 adverse events[*2]	
Lipase increased	5 (7.9)
Gamma-glutamyltransferase increased	5 (7.9)
Hepatic function abnormal	4 (6.3)
Hyperphosphataemia	3 (4.8)
Hyponatraemia	3 (4.8)
Adverse events leading to death[*3]	
Death	2 (3.2)
Serious adverse events[*3]	
Hepatic function abnormal	3 (4.8)
Death	2 (3.2)
Cancer pain	2 (3.2)
Adverse events leading to treatment interruption[*2]	
Nausea	3 (4.8)
Stomatitis	3 (4.8)
Pyrexia	3 (4.8)
Adverse events leading to dose reduction[*2]	
Palmar-plantar erythrodysaesthesia syndrome	8 (12.7)
Paronychia	4 (6.3)
Hyperphosphataemia	4 (6.3)
Corneal epithelium defect	3 (4.8)
Keratitis	3 (4.8)
Retinal detachment	3 (4.8)
Diarrhoea	3 (4.8)

*1, events reported in ≥20% of subjects; *2, events reported in ≥4% of subjects; *3, events reported in ≥3% of subjects.

PMDA's view:

The most common adverse events, Grade ≥3 adverse events, and serious adverse events reported in Study 201 are likely to occur during treatment with tasurgratinib, and these events should therefore be carefully monitored with consideration to their association with tasurgratinib treatment. Most of the reported events were manageable by taking measures such as interruption or dose reduction of tasurgratinib. In view of the above points, tasurgratinib will be tolerable if appropriate measures, such as monitoring and management of adverse events and interruption or dose reduction of tasurgratinib, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

7.R.3.2 Differences in safety between Japanese and non-Japanese patients

The applicant's explanation about differences in safety between Japanese and non-Japanese patients based on the safety information obtained in Study 201:

Table 26 summarizes safety in Japanese and non-Japanese patients in Study 201.

Table 26. Summary of safety (Study 201)

	n (%)	
	Japanese	Non-Japanese
	N = 28	N = 35
Any adverse event	28 (100)	35 (100)
Grade ≥3 adverse events	17 (60.7)	18 (51.4)
Adverse events leading to death	3 (10.7)	1 (2.9)
Serious adverse events	11 (39.3)	11 (31.4)
Adverse events leading to treatment discontinuation	2 (7.1)	4 (11.4)
Adverse events leading to treatment interruption	13 (46.4)	18 (51.4)
Adverse events leading to dose reduction	16 (57.1)	19 (54.3)

Table 27 shows adverse events reported more frequently in Japanese patients than in non-Japanese patients in Study 201. There were no adverse events leading to death, serious adverse events, or adverse events leading to treatment discontinuation with a ≥5% higher incidence in Japanese patients than in non-Japanese patients.

Table 27. Adverse events reported more frequently in Japanese patients than in non-Japanese patients (Study 201)

PT (MedDRA ver. 26.0)	n (%)	
	Japanese	Non-Japanese
	N = 28	N = 35
Any-grade adverse events[*1]		
Stomatitis	14 (50.0)	2 (5.7)
Paronychia	11 (39.3)	3 (8.6)
Pyrexia	10 (35.7)	4 (11.4)
Dysgeusia	9 (32.1)	2 (5.7)
Nausea	8 (28.6)	0
Grade ≥3 adverse events[*2]		
Lipase increased	3 (10.7)	2 (5.7)
Gamma-glutamyltransferase increased	3 (10.7)	2 (5.7)
Palmar-plantar erythrodysaesthesia syndrome	2 (7.1)	0
Adverse events leading to treatment interruption[*2]		
Nausea	3 (10.7)	0
Stomatitis	3 (10.7)	0
Decreased appetite	2 (7.1)	0
Adverse events leading to dose reduction[*2]		
Palmar-plantar erythrodysaesthesia syndrome	6 (21.4)	2 (5.7)
Paronychia	4 (14.3)	0
Diarrhoea	3 (10.7)	0
Stomatitis	2 (7.1)	0
Onycholysis	2 (7.1)	0
Nail bed bleeding	2 (7.1)	0

*1, events with a ≥20% higher incidence in Japanese patients; *2, events with a ≥5% higher incidence in Japanese patients.

PMDA's view:

Although some adverse events were reported more frequently in Japanese patients than in non-Japanese patients in Study 201, the incidences of Grade ≥3 adverse events and serious adverse events did not tend to be clearly higher in Japanese patients than in non-Japanese patients. In addition, tasurgratinib is expected to be

used by physicians with adequate knowledge and experience in cancer chemotherapy. In view of these, tasurgratinib is tolerable in Japanese patients as well.

In the following sections, PMDA reviewed the safety results of Study 201 with a focus on the most common adverse events in patients receiving tasurgratinib, potential adverse events suspected from the mechanism of action of tasurgratinib, and adverse events of special interest for pemigatinib and futibatinib, which target FGFR, as with tasurgratinib.

7.R.3.3 Hyperphosphatemia

The applicant's explanation about hyperphosphatemia associated with the use of tasurgratinib:
Events coded to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) "hyperphosphataemia" or "blood phosphorus increased" were classified as hyperphosphatemia.

In Study 201, serum phosphate concentrations were measured at screening, at 1-week intervals for 4 weeks after the start of treatment with tasurgratinib, and thereafter at ≥2-week intervals. Subjects with hyperphosphatemia were to undergo management with dietary therapy and phosphate-lowering therapy.

Table 28 and Table 29 show the incidences of hyperphosphatemia in Study 201. In Study 201, the median time (minimum, maximum) to the first onset of hyperphosphatemia was 8 (6, 205) days.

Table 28. Incidences of hyperphosphatemia (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63	
	Any grade	Grade ≥3
Hyperphosphatemia*	51 (81.0)	3 (4.8)
Hyperphosphataemia	51 (81.0)	3 (4.8)

* Total of events collected

Table 29. Incidences of serious hyperphosphatemia (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63
Hyperphosphatemia leading to death	0
Serious hyperphosphatemia	0
Hyperphosphatemia leading to treatment discontinuation	0
Hyperphosphatemia leading to treatment interruption	0
Hyperphosphatemia leading to dose reduction	4 (6.3)
Hyperphosphataemia	4 (6.3)

No serious hyperphosphatemia associated with tasurgratinib was observed in the clinical studies of tasurgratinib, including other studies than the one above.

PMDA's view:
Although no serious hyperphosphatemia was observed in clinical studies, hyperphosphatemia was frequently reported in Study 201, in which a management method for hyperphosphatemia was specified. In addition, hyperphosphatemia is an adverse event that can be anticipated from the mechanism of action of the FGFR

inhibitor, and is a known risk for other FGFR inhibitors. In view of these, attention should be paid to the occurrence of hyperphosphatemia during treatment with tasurgratinib. The applicant is therefore required to appropriately provide precautions to healthcare professionals, using the package insert and other materials, regarding the incidences of hyperphosphatemia in clinical studies and hyperphosphatemia management.

7.R.3.4 Retinal disorder

The applicant's explanation about retinal disorder associated with tasurgratinib:
Among the events coded to the primary MedDRA system organ class (SOC) "eye disorders," the MedDRA PTs including "retina," "macula," or "choroid" related disorders were classified as retinal disorder.

In Study 201, ophthalmological examination was performed at screening, at 2-week intervals for 4 weeks after the start of treatment with tasurgratinib, and thereafter at 8-week intervals.

Table 30 and Table 31 show the incidences of retinal disorder in Study 201. In Study 201, the median time (minimum, maximum) to the first onset of retinal disorder was 17.5 (12, 142) days.

Table 30. Incidences of retinal disorder (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63	
	Any grade	Grade ≥3
Retinal disorder*	26 (41.3)	1 (1.6)
Macular oedema	7 (11.1)	0
Retinal detachment	5 (7.9)	0
Serous retinal detachment	5 (7.9)	0
Subretinal fluid	3 (4.8)	0
Macular degeneration	2 (3.2)	1 (1.6)
Central serous chorioretinopathy	1 (1.6)	0
Epiretinal membrane	1 (1.6)	0
Macular detachment	1 (1.6)	0
Macular thickening	1 (1.6)	0
Maculopathy	1 (1.6)	0
Retinal haemorrhage	1 (1.6)	0
Retinopathy	1 (1.6)	0

* Total of events collected

Table 31. Incidences of serious retinal disorder (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63
Retinal disorder leading to death	0
Serious retinal disorder	0
Retinal disorder leading to treatment discontinuation	0
Retinal disorder leading to treatment interruption	4 (6.3)
Subretinal fluid	2 (3.2)
Macular degeneration	1 (1.6)
Retinal detachment	1 (1.6)
Retinal disorder leading to dose reduction	5 (7.9)
Retinal detachment	3 (4.8)
Macular degeneration	1 (1.6)
Macular detachment	1 (1.6)

No serious retinal disorder was observed in the clinical studies of tasurgratinib, including other studies than the one above.

PMDA's view:
Although no serious retinal disorder was observed in clinical studies, there were a certain number of cases of retinal detachment in Study 201 in which ophthalmological examination was periodically performed. Retinal detachment significantly affects the patient's daily life, and its early detection is therefore important. In addition, retinal detachment is an adverse event that can be anticipated from the mechanism of action of the FGFR inhibitor and is a known risk for other FGFR inhibitors. In view of these, attention should be paid to the occurrence of retinal detachment during treatment with tasurgratinib. The applicant is therefore required to appropriately provide precautions to healthcare professionals, using the package insert and other materials, regarding the incidences of retinal detachment in clinical studies, implementation of periodic ophthalmological examinations, and actions to be taken at the onset of retinal detachment.

7.R.3.5 Eye disorders (except for retinal disorder)

The applicant's explanation about eye disorders (except for retinal disorder) associated with tasurgratinib:
Among the events coded to the primary MedDRA SOC "eye disorders," the MedDRA PTs excluding "retina," "macula," or "choroid" related disorders were classified as eye disorders.

Table 32 and Table 33 show the incidences of eye disorders in Study 201. In Study 201, the median time (minimum, maximum) to the first onset of eye disorders was 85 (6, 566) days.

Table 32. Incidences of eye disorders reported in ≥2% of subjects (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63	
	Any grade	Grade ≥3
Eye disorders*	40 (63.5)	2 (3.2)
Keratitis	13 (20.6)	0
Dry eye	9 (14.3)	1 (1.6)
Corneal epithelium defect	8 (12.7)	1 (1.6)
Xerophthalmia	8 (12.7)	0
Vision blurred	5 (7.9)	1 (1.6)
Cataract	3 (4.8)	0
Corneal opacity	3 (4.8)	1 (1.6)
Punctate keratitis	2 (3.2)	0

* Total of events collected

Table 33. Incidences of serious eye disorders (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63
Eye disorders leading to death	0
Serious eye disorders	0
Eye disorders leading to treatment discontinuation	1 (1.6)
Corneal epithelium defect	1 (1.6)
Eye disorders leading to treatment interruption	4 (6.3)
Corneal opacity	2 (3.2)
Corneal epithelium defect	1 (1.6)
Corneal erosion	1 (1.6)
Vision blurred	1 (1.6)
Eye disorders leading to dose reduction	11 (17.5)
Corneal epithelium defect	3 (4.8)
Keratitis	3 (4.8)
Corneal opacity	2 (3.2)
Vision blurred	2 (3.2)
Corneal disorder	1 (1.6)
Corneal erosion	1 (1.6)
Dry eye	1 (1.6)
Optic nerve cupping	1 (1.6)
Refraction disorder	1 (1.6)
Xerophthalmia	1 (1.6)

Table 34 shows the details of patient with serious eye disorders in clinical studies of tasurgratinib, including other studies than the one above.

Table 34. List of patients with serious eye disorders

Study identifier	Age	Sex	PT[*1]	Grade[*2]	Time to onset (days)	Duration (days)	Disposition of tasurgratinib	Causal relationship to tasurgratinib	Outcome
003	2[redacted]	Male	Erythema of eyelid	Mild	4	26	Discontinuation	Related	Resolved
			Swelling of eyelid	Mild	4	26	Discontinuation	Related	Resolved

*1, MedDRA ver.24.0; *2, classified as mild if activities of daily living were not affected.

PMDA's view:

Since only a limited number of patients experienced Grade ≥3 or serious eye disorders in clinical studies, a definite conclusion regarding the risk of eye disorders associated with the use of tasurgratinib cannot be drawn at present. However, eye disorders significantly affect daily life. The applicant is therefore required to appropriately provide information using the package insert and other materials regarding the incidences of eye disorders in clinical studies, and continue collecting relevant information in the post-marketing setting. The applicant should also provide any new information appropriately to healthcare professionals when it becomes available.

7.R.3.6 Nail disorders

The applicant's explanation about nail disorders associated with tasurgratinib:

Among events coded to the MedDRA SOC "infections and infestations" or "skin and subcutaneous tissue disorders," the MedDRA PTs including nail-related disorders (except for the MedDRA PT "paronychia") were classified as nail disorders.

Table 35 and Table 36 show the incidences of nail disorders in Study 201. In Study 201, the median time (minimum, maximum) to the first onset of nail disorders was 46 (5, 144) days.

Table 35. Incidences of nail disorders (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63	
	Any grade	Grade ≥3
Nail disorders*	41 (65.1)	0
Nail discolouration	12 (19.0)	0
Onycholysis	12 (19.0)	0
Nail bed bleeding	10 (15.9)	0
Onychomadesis	7 (11.1)	0
Onychalgia	6 (9.5)	0
Nail disorder	3 (4.8)	0
Onychoclasis	3 (4.8)	0
Anonychia	2 (3.2)	0
Nail hypertrophy	2 (3.2)	0
Onychomycosis	1 (1.6)	0

* Total of events collected

Table 36. Incidences of serious nail disorders (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63
Nail disorders leading to death	0
Serious nail disorders	0
Nail disorders leading to treatment discontinuation	0
Nail disorders leading to treatment interruption	3 (4.8)
Onycholysis	2 (3.2)
Onychoclasis	1 (1.6)
Nail disorders leading to dose reduction	7 (11.1)
Nail bed bleeding	2 (3.2)
Onychalgia	2 (3.2)
Onycholysis	2 (3.2)
Anonychia	1 (1.6)
Nail hypertrophy	1 (1.6)

No serious nail disorders were observed in the clinical studies of tasurgratinib, including other studies than the one above.

PMDA's view:

Since no serious nail disorders were observed in clinical studies, a definite conclusion regarding the risk of nail disorders associated with the use of tasurgratinib cannot be drawn at present. However, nail disorders such as onycholysis and onychomadesis, which significantly affect daily life, were reported in a certain proportion of subjects. In view of this, the applicant is required to provide information, using the package insert and other materials, regarding the incidences of nail disorders in clinical studies, and continue collecting relevant information in the post-marketing setting. The applicant should also provide any new information appropriately to healthcare professionals when it becomes available.

7.R.3.7 Skin disorders

The applicant's explanation about skin disorders associated with the use of tasurgratinib:

Events coded to the primary MedDRA SOC "skin and subcutaneous tissue disorders" (except for the MedDRA PTs including nail-related disorders) and the MedDRA PT "paronychia" were classified as skin disorders.

Table 37 and Table 38 show the incidences of skin disorders in Study 201. In Study 201, the median time (minimum, maximum) to the first onset of skin disorders was 39.5 (7, 315) days.

Table 37. Incidences of skin disorders reported in ≥2% of subjects (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63	
	Any grade	Grade ≥3
Skin disorders*	42 (66.7)	2 (3.2)
Palmar-plantar erythrodysaesthesia syndrome	28 (44.4)	2 (3.2)
Paronychia	14 (22.2)	0
Alopecia	8 (12.7)	0
Rash	5 (7.9)	0
Dry skin	4 (6.3)	0
Hyperkeratosis	3 (4.8)	0
Pruritus	2 (3.2)	0
Skin fissures	2 (3.2)	0

* Total of events collected

Table 38. Incidences of serious skin disorders (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63
Skin disorders leading to death	0
Serious skin disorders	0
Skin disorders leading to treatment discontinuation	0
Skin disorders leading to treatment interruption	3 (4.8)
Palmar-plantar erythrodysaesthesia syndrome	2 (3.2)
Paronychia	1 (1.6)
Skin disorders leading to dose reduction	8 (12.7)
Palmar-plantar erythrodysaesthesia syndrome	8 (12.7)
Paronychia	4 (6.3)

Table 39 shows the details of patient with serious skin disorders in the clinical studies of tasurgratinib, including other studies than the one above.

Table 39. List of patients with serious skin disorders

Study identifier	Age	Sex	PT[*1]	Grade[*2]	Time to onset (days)	Duration (days)	Disposition of tasurgratinib	Causal relationship to tasurgratinib	Outcome
003	2[redacted]	Male	Eczema asteatotic	Mild	4	11	Unchanged	Related	Resolved

*1, MedDRA ver.24.0; *2, determined as mild if daily activities were not affected.

PMDA's view:

Since only a limited number of patients experienced serious skin disorders in clinical studies, a definite conclusion regarding the risk of skin disorders associated with tasurgratinib cannot be drawn at present. However, palmar-plantar erythrodysesthesia and similar disorders were reported in a certain proportion of

subjects after administration of tasurgratinib. In view of this, the applicant is required to provide information, using the package insert and other materials, regarding the incidences of skin disorders in clinical studies, and continue collecting relevant information in the post-marketing setting. The applicant should also provide any new information appropriately to healthcare professionals when it becomes available.

7.R.3.8 Others

(1) Hepatic function disorders

The applicant's explanation about hepatic function disorders associated with the use of tasurgratinib:

Events encoded to standardised MedDRA queries (SMQ) "drug related hepatic disorders - comprehensive search" but not to the primary MedDRA SOC "skin and subcutaneous tissue disorders," "injury, poisoning and procedural complications," or "surgical and medical procedures" were classified as hepatic function disorders.

Table 40 and Table 41 show the incidences of hepatic function disorders in Study 201. In Study 201, the median time (minimum, maximum) to the first onset of hepatic function disorders was 15 (1, 404) days.

Table 40. Incidences of hepatic function disorders reported in ≥3% of subjects (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63	
	Any grade	Grade ≥3
Hepatic function disorders*	39 (61.9)	13 (20.6)
Aspartate aminotransferase increased	20 (31.7)	2 (3.2)
Alanine aminotransferase increased	18 (28.6)	2 (3.2)
Blood alkaline phosphatase increased	13 (20.6)	2 (3.2)
Gamma-glutamyltransferase increased	9 (14.3)	5 (7.9)
Blood bilirubin increased	5 (7.9)	0
Hepatic function abnormal	5 (7.9)	4 (6.3)
Hypoalbuminaemia	4 (6.3)	0
Liver injury	3 (4.8)	1 (1.6)
Bilirubin conjugated increased	2 (3.2)	0
Hyperbilirubinaemia	2 (3.2)	0

* Total of events collected

Table 41. Incidences of serious hepatic function disorders (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63
Hepatic function disorders leading to death	0
Serious hepatic function disorders	5 (7.9)
Hepatic function abnormal	3 (4.8)
Ascites	1 (1.6)
Jaundice cholestatic	1 (1.6)
Hepatic function disorders for which a causal relationship to tasurgratinib could not be ruled out	1 (1.6)
Hepatic function abnormal	1 (1.6)
Hepatic function disorders leading to treatment discontinuation	1 (1.6)
Hepatic function abnormal	1 (1.6)
Hepatic function disorders leading to treatment interruption	3 (4.8)
Alanine aminotransferase increased	1 (1.6)
Hepatic function abnormal	1 (1.6)
Jaundice cholestatic	1 (1.6)
Liver injury	1 (1.6)
Hepatic function disorders leading to dose reduction	2 (3.2)
Alanine aminotransferase increased	1 (1.6)
Aspartate aminotransferase increased	1 (1.6)
Hepatic function abnormal	1 (1.6)

In the clinical studies of tasurgratinib, including other studies than the one above, serious hepatic function disorders were observed in 5 subjects. Table 42 shows the details of the patient with serious hepatic function disorders for which a causal relationship to tasurgratinib could not be ruled out.

Table 42. List of patients with serious hepatic function disorders for which a causal relationship to tasurgratinib could not be ruled out

Study identifier	Age	Sex	PT*	Grade	Time to onset (days)	Duration (days)	Disposition of tasurgratinib	Outcome
201	5[redacted]	Female	Hepatic function abnormal	3	91	12	Dose reduction	Resolved

*: MedDRA ver. 26.0

In clinical studies using tasurgratinib, there were no hepatic function disorders meeting the Hy's law criteria for laboratory data (defined based on the Guidance for industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009).

PMDA's view:

Although hepatic function disorders were reported in a certain proportion of subjects in clinical studies, the number of subjects with serious hepatic function disorders for which a causal relationship to tasurgratinib could not be ruled out was limited, and the reported events resolved with dose reduction of tasurgratinib. In view of this, no particular precautions against hepatic function disorders are required at present, on the premise that the applicant provides information, using the package insert and other materials, regarding the incidences of hepatic function disorders in clinical studies, continues collecting relevant information in the post-marketing setting, and communicates any new information to healthcare professionals when it becomes available.

(2) Renal function disorders

The applicant's explanation about renal function disorders associated with the use of tasurgratinib:

Events coded to the MedDRA SMQ "acute renal failure (broad)" or MedDRA PT "renal failure" (except for those coded to the primary MedDRA SOC "surgical and medical procedures") were classified as renal function disorders.

Table 43 shows the incidences of renal function disorders in Study 201. In Study 201, the median time (minimum, maximum) to the first onset of renal function disorders was 43 (7, 166) days.

Table 43. Incidences of renal function disorders reported in ≥2% of subjects (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63	
	Any grade	Grade ≥3
Renal function disorders*	20 (31.7)	0
Blood creatinine increased	13 (20.6)	0
Proteinuria	4 (6.3)	0
Blood urea increased	3 (4.8)	0
Albuminuria	2 (3.2)	0
Protein urine present	2 (3.2)	0

* Total of events collected

In Study 201, there were no renal function disorders leading to death, serious renal function disorders, renal function disorders leading to treatment discontinuation, renal function disorders leading to treatment interruption, or renal function disorders leading to dose reduction.

No serious renal function disorders were observed in the clinical studies of tasurgratinib, including other studies than the one above.

PMDA's view:

Although renal function disorders were reported in a certain proportion of subjects in clinical studies, there were no Grade ≥3 or serious renal function disorders. In view of this, no particular precautions against renal function disorders are required at present, on the premise that the applicant provides information, using the package insert and other materials, regarding the incidences of renal function disorders in clinical studies, continues collecting relevant information in the post-marketing setting, and communicates any new information to healthcare professionals when it becomes available.

(3) Gastrointestinal disorders

The applicant's explanation about gastrointestinal disorders associated with the use of tasurgratinib:

Events coded to the primary MedDRA SOC "gastrointestinal disorders" were classified as gastrointestinal disorders.

Table 44 and Table 45 show the incidences of gastrointestinal disorders in Study 201. In Study 201, the median time (minimum, maximum) to the first onset of gastrointestinal disorders was 16 (1, 269) days.

Table 44. Incidences of gastrointestinal disorders reported in ≥2% of subjects (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63	
	Any grade	Grade ≥3
Gastrointestinal disorders*	49 (77.8)	4 (6.3)
Diarrhoea	23 (36.5)	0
Stomatitis	16 (25.4)	1 (1.6)
Dry mouth	14 (22.2)	0
Constipation	8 (12.7)	0
Nausea	8 (12.7)	0
Vomiting	8 (12.7)	0
Abdominal pain	4 (6.3)	0
Mouth ulceration	4 (6.3)	0
Abdominal distension	3 (4.8)	0
Abdominal pain upper	3 (4.8)	0
Oesophagitis	2 (3.2)	0

* Total of events collected

Table 45. Incidences of serious gastrointestinal disorders (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63
Gastrointestinal disorders leading to death	0
Serious gastrointestinal disorders	6 (9.5)
Abdominal pain	1 (1.6)
Ascites	1 (1.6)
Intestinal obstruction	1 (1.6)
Large intestinal haemorrhage	1 (1.6)
Pancreatitis	1 (1.6)
Stomatitis	1 (1.6)
Gastrointestinal disorders for which a causal relationship to tasurgratinib could not be ruled out	2 (3.2)
Abdominal pain	1 (1.6)
Stomatitis	1 (1.6)
Gastrointestinal disorders leading to treatment discontinuation	1 (1.6)
Stomatitis	1 (1.6)
Gastrointestinal disorders leading to treatment interruption	6 (9.5)
Nausea	3 (4.8)
Stomatitis	3 (4.8)
Abdominal pain	1 (1.6)
Constipation	1 (1.6)
Intestinal obstruction	1 (1.6)
Large intestinal haemorrhage	1 (1.6)
Gastrointestinal disorders leading to dose reduction	5 (7.9)
Diarrhoea	3 (4.8)
Stomatitis	2 (3.2)
Nausea	1 (1.6)

In the clinical studies of tasurgratinib, including other studies than the one above, serious gastrointestinal disorders were observed in 7 subjects. Table 46 shows the details of patients with serious gastrointestinal disorders for which a causal relationship to tasurgratinib could not be ruled out.

Table 46. List of patients with serious gastrointestinal disorders for which a causal relationship to tasurgratinib could not be ruled out

Study identifier	Age	Sex	PT*	Grade	Time to onset (days)	Duration (days)	Disposition of tasurgratinib	Outcome
201	4[redacted]	Female	Abdominal pain	1	302	34	Interruption	Resolved
	6[redacted]	Male	Stomatitis	2	87	Unknown	Discontinuation	Not resolved

*: MedDRA ver. 26.0

PMDA's view:

Although gastrointestinal disorders were reported in a certain proportion of subjects in clinical studies, most of the events were Grade ≤2, and the number of subjects with serious gastrointestinal disorders for which a causal relationship to tasurgratinib could not be ruled out was limited. In view of this, no particular precautions against gastrointestinal disorders are required at present, on the premise that the applicant provides information, using the package insert and other materials, regarding the incidences of gastrointestinal disorders in clinical studies, continues collecting relevant information in the post-marketing setting, and communicates any new information to healthcare professionals when it becomes available.

(4) Hemorrhage

The applicant's explanation about hemorrhage associated with the use of tasurgratinib:

Events coded to MedDRA SMQ "haemorrhages (narrow)" were classified as hemorrhage.

Table 47 and Table 48 show the incidences of hemorrhage in Study 201. In Study 201, the median time (minimum, maximum) to the first onset of hemorrhage was 35 (5, 379) days.

Table 47. Incidences of hemorrhage (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63	
	Any grade	Grade ≥3
Hemorrhage*	21 (33.3)	1 (1.6)
Nail bed bleeding	10 (15.9)	0
Epistaxis	9 (14.3)	0
Conjunctival haemorrhage	1 (1.6)	0
Gingival bleeding	1 (1.6)	0
Haematuria	1 (1.6)	0
Haemoptysis	1 (1.6)	1 (1.6)
Large intestinal haemorrhage	1 (1.6)	0
Oral blood blister	1 (1.6)	0
Retinal haemorrhage	1 (1.6)	0
Urinary occult blood positive	1 (1.6)	0

* Total of events collected

Table 48. Incidences of serious hemorrhage (Study 201)

PT (MedDRA ver. 26.0)	n (%) N = 63
Hemorrhage leading to death	0
Serious hemorrhage	2 (3.2)
Haemoptysis	1 (1.6)
Large intestinal haemorrhage	1 (1.6)
Hemorrhage for which a causal relationship to tasurgratinib could not be ruled out	1 (1.6)
Haemoptysis	1 (1.6)
Hemorrhage leading to treatment discontinuation	1 (1.6)
Haemoptysis	1 (1.6)
Hemorrhage leading to treatment interruption	2 (3.2)
Haemoptysis	1 (1.6)
Large intestinal haemorrhage	1 (1.6)
Hemorrhage leading to dose reduction	3 (4.8)
Nail bed bleeding	2 (3.2)
Haemoptysis	1 (1.6)

In the clinical studies of tasurgratinib, including other studies than the one above, serious hemorrhage was observed in 2 subjects. Table 49 shows the details of the patient with serious hemorrhage for which a causal relationship to tasurgratinib could not be ruled out.

Table 49. List of patients with serious hemorrhage for which a causal relationship to tasurgratinib could not be ruled out

Study identifier	Age	Sex	PT*	Grade	Time to onset (days)	Duration (days)	Disposition of tasurgratinib	Outcome
201	5[redacted]	Female	Haemoptysis	3	103	9	Dose reduction	Resolved

*: MedDRA ver. 26.0

PMDA's view:

Although hemorrhage was reported in a certain proportion of subjects in clinical studies, most of the events were Grade ≤2. The number of subjects with serious hemorrhage for which a causal relationship to tasurgratinib could not be ruled out was limited, and the reported events resolved with dose reduction of tasurgratinib. In view of this, no particular precautions against hemorrhage are required at present, on the premise that the applicant provides information, using the package insert and other materials, regarding the incidences of hemorrhage in clinical studies, continues collecting relevant information in the post-marketing setting, and communicates any new information to healthcare professionals when it becomes available.

7.R.4 Clinical positioning and indication

The proposed indication of tasurgratinib was "unresectable biliary tract cancer with *FGFR2* gene fusion in patients who have received prior cancer chemotherapy." The applicant explained that after submission of the present application, the following statements would be included in the "Precautions Concerning Indication" section:

- The efficacy and safety of tasurgratinib as the first-line therapy have not been established.
- The efficacy and safety of tasurgratinib have not been established for adjuvant chemotherapy.
- Eligible patients should be identified by physicians with a full understanding of the information on patients enrolled in clinical studies (e.g., location of the primary lesion) presented in the "Clinical Studies" section and of the efficacy and safety of tasurgratinib.

- Tasurgratinib can be used in patients with *FGFR2* gene fusion confirmed by adequately experienced pathologists or by testing at laboratories with extensive expertise. The testing should be performed using approved *in vitro* diagnostics or medical devices.

As a result of the reviews presented in Sections "7.R.2 Efficacy" and "7.R.3 Safety," as well as the subsections below, PMDA has concluded that the indication of tasurgratinib should be "unresectable biliary tract cancer with *FGFR2* gene fusion that has progressed after cancer chemotherapy," with the proposed precautionary statements included in the "Precautions Concerning Indication" section.

7.R.4.1 Clinical positioning of tasurgratinib and intended population

Japanese and foreign clinical practice guidelines and representative textbooks on clinical oncology provide no descriptions about the use of tasurgratinib in the treatment of unresectable biliary tract cancer.

The applicant's explanation about the intended patient population and indication of tasurgratinib:
In view of the results of Study 201 and other studies, tasurgratinib can be positioned as a treatment option for patients with unresectable cholangiocarcinoma with *FGFR2* gene fusion who have received prior chemotherapy. Although confirmed response was not observed in 2 patients with hilar cholangiocarcinoma enrolled in Study 201, one of them showed PR (non-confirmed response), and the tumors in both patients tended to shrink (−6.7% and −31.8%). In view of this, tasurgratinib is expected to have efficacy in the treatment of patients with hilar cholangiocarcinoma as well.

Patients with some subtypes of biliary tract cancer, namely, distal cholangiocarcinoma, gallbladder cancer, and papillary carcinoma, were not included in Study 201, and no clinical study results on the efficacy or safety of tasurgratinib in these patients are available. However, given that (a) the treatment algorithms for unresectable intrahepatic or hilar cholangiocarcinoma, distal cholangiocarcinoma, gallbladder cancer, and papillary carcinoma are similar, and (b) it is difficult to conduct studies for each location of the primary lesion because *FGFR2* gene fusion-positive distal cholangiocarcinoma, gallbladder cancer, and papillary carcinoma are very rare (*Hepatology*. 2014;59:1427-1434, *J Gastroenterol*. 2021;56:250-260, etc.), the use of tasurgratinib in these patient population is acceptable. Nevertheless, the efficacy of tasurgratinib has not been established in patients with distal cholangiocarcinoma, gallbladder cancer, or papillary carcinoma; therefore, eligible patients for treatment with tasurgratinib should be identified by physicians with a full understanding of the above information.

In addition, the "Indication" section should clearly state that tasurgratinib is indicated for patients who have received prior cancer chemotherapy, because Study 201 enrolled patients who had received prior chemotherapy, and no clinical study results on the efficacy or safety of tasurgratinib in patients who have not received prior chemotherapy are available.

Since no clinical study results on the efficacy or safety of tasurgratinib are available for adjuvant chemotherapy, tasurgratinib is not recommended for adjuvant chemotherapy.

On the basis of the above, the indication of tasurgratinib was specified as "unresectable biliary tract cancer with *FGFR2* gene fusion in patients who have received prior cancer chemotherapy," with details of the patient population enrolled in Study 201 (e.g., location of the primary lesion) presented in the "Clinical Studies" section and the following precautionary statements provided in the "Precautions Concerning Indication" section of the package insert:

- The efficacy and safety of tasurgratinib as the first-line therapy have not been established.
- The efficacy and safety of tasurgratinib have not been established for adjuvant chemotherapy.
- Eligible patients should be identified by physicians with a full understanding of the information on patients enrolled in clinical studies (e.g., location of the primary lesion) presented in the "Clinical Studies" section and of the efficacy and safety of tasurgratinib.

The choice among FGFR inhibitors, i.e., tasurgratinib, pemigatinib, and futibatinib, for use in patients with unresectable biliary tract cancer with *FGFR2* gene fusion who have received prior chemotherapy has yet to be clarified because no clinical study results comparing the efficacy or safety of tasurgratinib with those of pemigatinib or futibatinib are available. Therefore, a suitable drug should be individually chosen considering the clinical pharmacologic characteristics of each drug.

PMDA's view:
PMDA largely accepted the applicant's explanation. However, treatment for patients with unresectable biliary tract cancer who have received prior chemotherapy is intended for use in patients with cancer that has progressed after chemotherapy. Therefore, the "Indication" section should clearly state that tasurgratinib is indicated for patients with cancer that has progressed after cancer chemotherapy, as with the indication of the FGFR inhibitors approved in Japan.

On the basis of the above, the indication of tasurgratinib should be "unresectable biliary tract cancer with *FGFR2* gene fusion that has progressed after cancer chemotherapy," with details of the patient population enrolled in Study 201 (e.g., location of the primary lesion) presented in the "Clinical Studies" section and the proposed statements provided in the "Precautions Concerning Indication" section of the package insert.

7.R.4.2 Testing of *FGFR2* gene fusions

An application for "AmoyDx FGFR2 Gene Break-apart FISH Probe Kit," a companion diagnostic used in support of eligibility assessment for tasurgratinib treatment, has been submitted by Nihon Stery, Inc.

The applicant's explanation about testing for *FGFR2* gene fusions, which is used to identify patients eligible for tasurgratinib treatment:
In Study 201, "AmoyDx FGFR2 Gene Break-apart FISH Probe Kit" of Amoy Diagnostics was used to identify *FGFR2* gene fusion-positive patients. Therefore, "AmoyDx FGFR2 Gene Break-apart FISH Probe Kit" should be used to identify patients for tasurgratinib treatment. The "Indication" section will include a statement to that effect.

PMDA accepted the applicant's explanation.

7.R.5 Dosage and administration

The proposed dosage and administration of tasurgratinib was "The usual adult dosage is 140 mg of tasurgratinib administered orally once daily. The dose may be reduced according to the patient's condition." The following statements were proposed for the "Precautions Concerning Dosage and Administration" section:

- The efficacy and safety of tasurgratinib have not been established for its use in combination with other antineoplastic agents.
- Administration of tasurgratinib after a high-fat meal should be avoided because it has been reported that the C_{max} and AUC of tasurgratinib following administration after a high-fat meal were lower than those following administration in the fasted state.
- Guide for treatment interruption, dose reduction, and treatment discontinuation of tasurgratinib in response to the onset of adverse drug reactions [see Section 7.R.5.2].

As a result of the reviews presented in Sections "6.R.1 Food effect," "7.R.2 Efficacy," "7.R.3 Safety," and the subsections below, PMDA has concluded that the dosage and administration of tasurgratinib should be "The usual adult dosage is 140 mg of tasurgratinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition," with the following precautionary statements provided in the "Precautions Concerning Dosage and Administration" section:

- The efficacy and safety of tasurgratinib have not been established for its use in combination with other antineoplastic agents.
- It has been reported that the C_{max} and AUC of tasurgratinib decreased following administration with food. To prevent the effect of food, administration of tasurgratinib should be avoided within 1 hour before and 2 hours after a meal.
- Guide for treatment interruption, dose reduction, and treatment discontinuation of tasurgratinib in response to the onset of adverse drug reactions [see Section 7.R.5.2].

7.R.5.1 Dosage and administration of tasurgratinib

The applicant's explanation about the rationale for the dosage and administration of tasurgratinib:

Study 201 was conducted using a dosage regimen based on the clinical study results presented below, tasurgratinib showed a certain level of efficacy and safety in the target patient population of the study. Therefore, the dosage and administration of tasurgratinib was decided based on the dosage regimen employed in Study 201.

- In Part 1 of Study 101, tasurgratinib was administered at 1 to 180 mg QD, and DLT was observed at 180 mg QD in 1 of 2 subjects (Grade 3 ALT increased and AST increased). However, MTD was not determined.
- In Part 2 of Study 101, the tolerability and a certain level of efficacy[61)] of tasurgratinib 140 mg QD were

[61)] Confirmed response was observed in 4 of 6 subjects.

confirmed in patients with unresectable biliary tract cancer with *FGFR2* gene fusion.

At the start of Study 201, the results of Part A of the Japanese phase I study (Study 003) to investigate the effect of food on the PK of tasurgratinib were not available. Therefore, tasurgratinib was administered in the fasted state in Study 201. However, in view of the following points, the applicant considers it unnecessary to specify the timing of tasurgratinib administration relative to meal intake:

- Since Part A of the Japanese phase I study (Study 003) showed that exposure decreased following administration of tasurgratinib 140 mg after a high-fat meal, compared with that following administration in the fasted state [see Section 6.1.1.1], administration of tasurgratinib after a high-fat meal is not recommended. However, no clear relationship was observed between tasurgratinib exposure and efficacy, and the decreased tasurgratinib exposure observed following administration after a high-fat meal is considered to have a limited impact on the efficacy of tasurgratinib.
- Although no clinical studies were conducted to investigate the effect of a low-fat meal on the PK of tasurgratinib, the effect of a low-fat meal on the PK of tasurgratinib is considered to be smaller than that of a high-fat meal.

No data from clinical studies investigating the efficacy and safety of tasurgratinib for its use in combination with other antineoplastic agents are available at present. Therefore, coadministration of tasurgratinib with other antineoplastic agents is not recommended.

PMDA's view:
As a result of the review presented in Section "6.R.1 Food effect," PMDA considers that tasurgratinib should be administered in the fasted state.

On the basis of the above, the dosage and administration of tasurgratinib should be, "The usual adult dosage is 140 mg of tasurgratinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition," with the following precautionary statements provided in the "Precautions Concerning Dosage and Administration" section:

- The efficacy and safety of tasurgratinib have not been established for its use in combination with other antineoplastic agents.
- It has been reported that the C_{max} and AUC of tasurgratinib decreased following administration with food. To prevent the effect of food, administration of tasurgratinib should be avoided within 1 hour before and 2 hours after a meal.

7.R.5.2 Dose adjustment of tasurgratinib

The applicant's explanation about the dose adjustment of tasurgratinib:
In Study 201, the criteria for dose adjustment of tasurgratinib were specifically defined, and tasurgratinib showed a certain level of efficacy and safety in patients who were treated in accordance with the criteria. Therefore, the criteria for dose adjustment were developed based on those in Study 201 and included in the "Precautions Concerning Dosage and Administration" section.

PMDA's view:

The above applicant's explanation is acceptable. The guide and criteria for dose adjustment should be modified as presented below and then included in the "Precautions Concerning Dosage and Administration" section.

- If any adverse reaction to tasurgratinib occurs, tasurgratinib should be interrupted, reduced in dose, or discontinued in accordance with the following criteria:

Guide for dose reduction

Dose reduction level	Dose
Usual dose	140 mg
1-level reduced dose	105 mg
2-level reduced dose	70 mg
3-level reduced dose	35 mg
4-level reduced dose	Discontinuation

Criteria for interruption, dose reduction, and discontinuation in response to adverse drug reactions

Adverse drug reaction	Severity*	Action
Hyperphosphatemia	Serum phosphate levels ≥5.5 mg/dL and ≤7.0 mg/dL	Initiate dietary therapy and/or phosphate-lowering therapy.
	Serum phosphate levels ≥7.1 mg/dL and ≤9.0 mg/dL	Initiate dietary therapy and/or phosphate-lowering therapy. If serum phosphate levels are ≥7.1 mg/dL for 2 weeks, interrupt tasurgratinib until the level returns to ≤7.0 mg/dL. Thereafter, to resume tasurgratinib, reduce the dose to the next lower level.
	Serum phosphate levels ≥9.1 mg/dL	Initiate dietary therapy and/or phosphate-lowering therapy. Interrupt tasurgratinib until the serum phosphate level returns to ≤7.0 mg/dL. To resume tasurgratinib, reduce the dose to the next lower level.
Corneal disorder and retinal disorder	Intolerable Grade 2, or Grade 3	Interrupt tasurgratinib until the event resolves to baseline or Grade ≤1. To resume tasurgratinib, reduce the dose to the next lower level.
	Grade 4	Discontinue tasurgratinib.
Blood disorders	Grade 3	Interrupt tasurgratinib until the event resolves to Grade ≤2. Resume tasurgratinib at the same dose level as that before the interruption.
	Grade 4	Interrupt tasurgratinib until the event resolves to Grade ≤2. To resume tasurgratinib, reduce the dose to the next lower level.
Other adverse drug reactions	Intolerable Grade 2	Interrupt tasurgratinib until the event resolves to baseline or Grade ≤1. To resume tasurgratinib, reduce the dose to the next lower level. Initial dose reduction (from 140 mg to 105 mg) does not require treatment interruption.
	Grade 3	Interrupt tasurgratinib until the event resolves to baseline or Grade ≤1. To resume tasurgratinib, reduce the dose to the next lower level.
	Grade 4 (in cases where non-life-threatening laboratory abnormalities occur, take the same action as that for Grade 3)	Discontinue tasurgratinib.

*: Graded according to NCI-CTCAE ver.4.03.

7.R.6 Post-marketing investigations

The applicant's explanation about the post-marketing surveillance plan:

The applicant plans to conduct a post-marketing surveillance in all patients treated with tasurgratinib to investigate the safety and other parameters of tasurgratinib during post-marketing clinical use.

The safety specification of the surveillance was defined as adverse events requiring special attention during treatment with tasurgratinib, namely, hyperphosphatemia, retinal disorder, and eye disorders (except for retinal disorder), based on the incidences of adverse events in Study 201.

The planned sample size and observation period of the surveillance are 62 patients and 1 year, respectively, based on the incidences of the above events (those to be included in the safety specification of the surveillance) in Study 201.

PMDA's view:
Post-marketing surveillance should be conducted to collect information on the safety of tasurgratinib during post-marketing clinical use for the following reasons:

- Post-marketing experience and safety information of tasurgratinib are not available in or outside of Japan.
- The number of subjects who received tasurgratinib (including Japanese patients) in the clinical studies submitted as efficacy and safety evaluation data was smaller than that with pemigatinib/futibatinib, and the safety profile of tasurgratinib, including the significant adverse drug reaction of retinal detachment, should be further clarified.

However, the need to conduct a post-marketing all-case surveillance is low in view of the following points:

- For FGFR inhibitors approved in Japan, a certain amount of safety information is available from the past experience in and outside of Japan, and there are no clear differences between these FGFR inhibitors and tasurgratinib.
- Although information on the safety of tasurgratinib in Japanese patients is limited, no concerns have been identified regarding differences in the safety of tasurgratinib between Japanese and non-Japanese patients [see Section 7.R.3.2].

On the basis of the review presented in Section "7.R.3 Safety," the safety specification of the surveillance should be defined as hyperphosphatemia, retinal detachment, eye disorders (except for retinal detachment), nail disorders, and palmar-plantar erythrodysesthesia syndrome, and information should be collected including that on the safety of tasurgratinib in patients with hepatic impairment.

The planned sample size and observation period of the surveillance should be reconsidered based on the incidences of the above events that should be included in the safety specification of the surveillance.

7.2 Adverse events observed in clinical studies

Deaths reported in the data submitted for safety evaluation were summarized in Section "7.1 Evaluation data." The following subsections summarize the most common adverse events other than deaths.

7.2.1 Japanese phase I study (Study 101)

7.2.1.1 Part 1

Adverse events were observed in 2 of 2 subjects (100%) in (a) the 1 mg group, 1 of 2 subjects (50.0%) in (b) the 2 mg group, 1 of 2 subjects (50.0%) in (c) the 4 mg group, 2 of 2 subjects (100%) in (d) the 8 mg group, 2 of 2 subjects (100%) in (e) the 16 mg group, (f) 2 of 2 subjects (100%) in the 30 mg group, 3 of 3 subjects (100%) in (g) the 60 mg group, 3 of 3 subjects (100%) in (h) the 100 mg group, 3 of 3 subjects (100%) in (i) the 140 mg group, and 3 of 3 subjects (100%) in (j) the 180 mg group. Adverse events for which a causal

relationship to tasurgratinib could not be ruled out were observed in 0 of 2 subjects in (a), 1 of 2 subjects (50.0%) in (b), 1 of 2 subjects (50.0%) in (c), 1 of 2 subjects (50.0%) in (d), 2 of 2 subjects (100%) in (e), 1 of 2 subjects (50.0%) in (f), 3 of 3 subjects (100%) in (g), 3 of 3 subjects (100%) in (h), 3 of 3 subjects (100%) in (i), and 3 of 3 subjects (100%) in (j). Adverse events observed in ≥50% of subjects in each group were constipation, insomnia, genital haemorrhage, and dry skin in 1 subject (50.0%) each in (a); nausea, constipation, vomiting, abdominal distension, decreased appetite, atelectasis, and rash in 1 subject (50.0%) each in (b); abdominal distension and upper respiratory tract infection in 1 subject (50.0%) each in (c); tumour pain in 2 subjects (100%), and constipation, fatigue, contusion, blood creatinine increased, insomnia, cough, and dyspnoea in 1 subject (50.0%) each in (d); leukopenia, fatigue, pyrexia, blood creatinine increased, lipase increased, hypercalcaemia, hypophosphataemia, tumour pain, and agitation in 1 subject (50.0%) each in (e); nausea in 2 subjects (100%), and pyrexia, fatigue, skin infection, platelet count decreased, neck pain, and tumour pain in 1 subject (50.0%) each in (f); diarrhoea and blood creatinine increased in 2 subjects (66.7%) each in (g); hyperphosphataemia in 3 subjects (100%), and serous retinal detachment and pyrexia in 2 subjects (66.7%) each in (h); blood creatinine increased, ALT increased and hyperphosphataemia in 3 subjects (100%) each, and diarrhoea, AST increased, blood ALP increased, and dysgeusia in 2 subjects (66.7%) each in (i); and diarrhoea and hyperphosphataemia in 3 subjects (100%) each, and nausea, ALT increased, AST increased, neutrophil count decreased, and palmar-plantar erythrodysaesthesia syndrome in 2 subjects (66.7%) each in (j).

Serious adverse events were observed in 0 subjects in (a), 0 subjects in (b), 0 subjects in (c), 2 of 2 subjects (100%) in (d), 0 subjects in (e), 1 of 2 subjects (50.0%) in (f), 0 subjects in (g), 0 subjects in (h), 0 subjects in (i), and 0 subjects in (j). The serious adverse events observed were tumour pain and dyspnoea in 1 subject (50.0%) each in (d), and pyrexia in 1 subject (50.0%) in (f), and a causal relationship to tasurgratinib was ruled out for all of these events.

There were no adverse events leading to treatment discontinuation of tasurgratinib.

7.2.1.2 Part 2

Adverse events were observed in all subjects, and adverse events for which a causal relationship to tasurgratinib could not be ruled out were also observed in all subjects. Table 50 shows adverse events reported in ≥30% of patients with gastric cancer or cholangiocarcinoma.

Table 50. Adverse events reported in ≥30% of patients with gastric cancer or cholangiocarcinoma

SOC PT (MedDRA ver. 26.0)	n (%)			
	Patients with gastric cancer N = 10		Patients with cholangiocarcinoma N = 6	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any adverse event	10 (100)	7 (70.0)	6 (100)	4 (66.7)
Blood and lymphatic system disorders				
Anaemia	4 (40.0)	2 (20.0)	0	0
Eye disorders				
Dry eye	0	0	2 (33.3)	0
Gastrointestinal disorders				
Diarrhoea	2 (20.0)	0	4 (66.7)	1 (16.7)
Stomatitis	3 (30.0)	0	3 (50.0)	0
Abdominal distension	3 (30.0)	1 (10.0)	1 (16.7)	0
General disorders and administration site conditions				
Pyrexia	1 (10.0)	0	2 (33.3)	0
Infections and infestations				
Paronychia	5 (50.0)	0	4 (66.7)	0
Investigations				
Blood creatinine increased	3 (30.0)	0	2 (33.3)	0
Aspartate aminotransferase increased	3 (30.0)	2 (20.0)	1 (16.7)	0
Alanine aminotransferase increased	3 (30.0)	1 (10.0)	0	0
Blood alkaline phosphatase increased	3 (30.0)	2 (20.0)	0	0
Lipase increased	0	0	2 (33.3)	2 (33.3)
Metabolism and nutrition disorders				
Hyperphosphataemia	10 (100)	0	6 (100)	0
Decreased appetite	5 (50.0)	1 (10.0)	2 (33.3)	1 (16.7)
Hypoalbuminaemia	3 (30.0)	1 (10.0)	0	0
Hypophosphataemia	0	0	2 (33.3)	1 (16.7)
Nervous system disorders				
Dysgeusia	4 (40.0)	0	2 (33.3)	0
Headache	0	0	2 (33.3)	1 (16.7)
Skin and subcutaneous tissue disorders				
Palmar-plantar erythrodysaesthesia syndrome	4 (40.0)	0	6 (100)	0
Dry skin	0	0	3 (50.0)	0

Serious adverse events were observed in 4 of 10 patients with gastric cancer (40.0%) and 1 of 6 patients with cholangiocarcinoma (16.7%). The serious adverse events observed in patients with gastric cancer were pyrexia, cholecystitis acute, pneumonia, septic shock, decreased appetite, tumour obstruction, tumour pain, and depressed level of consciousness in 1 subject (10.0%) each, and those observed in patients with cholangiocarcinoma were ileus, cholangitis and thrombophlebitis migrans in 1 subject (16.7%) each. A causal relationship to tasurgratinib was ruled out for all of these events.

Adverse events leading to tasurgratinib treatment discontinuation were observed in 1 of 10 patients with gastric cancer (10.0%) and 0 patients with cholangiocarcinoma. The adverse events leading to tasurgratinib treatment discontinuation observed were cholecystitis acute and septic shock in 1 patient with gastric cancer (10.0%) each, and a causal relationship to tasurgratinib was ruled out for both of these events.

7.2.2 Global phase II study (Study 201)

Adverse events were observed in all subjects, and adverse events for which a causal relationship to tasurgratinib could not be ruled out were observed in 61 (96.8%) of 63 subjects. Table 51 shows adverse events reported in ≥10% of subjects.

Table 51. Adverse events reported in ≥10% of subjects

SOC PT (MedDRA ver. 26.0)	n (%) N = 63	
	Any grade	Grade ≥3
Any adverse event	63 (100)	35 (55.6)
Eye disorders		
Keratitis	13 (20.6)	0
Dry eye	9 (14.3)	0
Corneal epithelium defect	8 (12.7)	1 (1.6)
Xerophthalmia	8 (12.7)	1 (1.6)
Macular oedema	7 (11.1)	0
Gastrointestinal disorders		
Diarrhoea	23 (36.5)	0
Stomatitis	16 (25.4)	1 (1.6)
Dry mouth	14 (22.2)	0
Constipation	8 (12.7)	0
Nausea	8 (12.7)	0
Vomiting	8 (12.7)	0
General disorders and administration site conditions		
Pyrexia	14 (22.2)	0
Infections and infestations		
Paronychia	14 (22.2)	0
Investigations		
Aspartate aminotransferase increased	20 (31.7)	2 (3.2)
Alanine aminotransferase increased	18 (28.6)	2 (3.2)
Blood alkaline phosphatase increased	13 (20.6)	2 (3.2)
Blood creatinine increased	13 (20.6)	0
Lipase increased	13 (20.6)	5 (7.9)
Neutrophil count decreased	10 (15.9)	2 (3.2)
White blood cell count decreased	10 (15.9)	1 (1.6)
Gamma-glutamyltransferase increased	9 (14.3)	5 (7.9)
Platelet count decreased	7 (11.1)	1 (1.6)
Metabolism and nutrition disorders		
Hyperphosphataemia	51 (81.0)	3 (4.8)
Decreased appetite	9 (14.3)	1 (1.6)
Hyponatraemia	8 (12.7)	3 (4.8)
Hypercalcaemia	7 (11.1)	2 (3.2)
Hyperuricaemia	7 (11.1)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	7 (11.1)	1 (1.6)
Nervous system disorders		
Dysgeusia	11 (17.5)	0
Respiratory, thoracic and mediastinal disorders		
Epistaxis	9 (14.3)	0
Skin and subcutaneous tissue disorders		
Palmar-plantar erythrodysaesthesia syndrome	28 (44.4)	2 (3.2)
Nail discolouration	12 (19.0)	0
Onycholysis	12 (19.0)	0
Nail bed bleeding	10 (15.9)	0
Alopecia	8 (12.7)	0
Onychomadesis	7 (11.1)	0

Serious adverse events were observed in 22 of 63 subjects (34.9%). Serious adverse events reported in ≥2 subjects were hepatic function abnormal in 3 subjects (4.8%), and death and cancer pain in 2 subjects (3.2%) each, and a causal relationship to tasurgratinib was not ruled out for hepatic function abnormal in 1 subject (1.6%).

Adverse events leading to tasurgratinib treatment discontinuation were observed in 6 of 63 subjects (9.5%). None of the adverse events leading to tasurgratinib treatment discontinuation were reported in ≥2 subjects.

8. Results of Compliance Assessment Concerning the New Drug Application Data and the Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that tasurgratinib has a certain level of efficacy in the treatment of unresectable biliary tract cancer with *FGFR2* gene fusion that has progressed after cancer chemotherapy, and that tasurgratinib has acceptable safety in view of its benefits. Tasurgratinib is a drug with a new active ingredient that is presumed to inhibit FGFR tyrosine kinase and is considered a clinically meaningful treatment option for patients with unresectable biliary tract cancer with *FGFR2* gene fusion that has progressed after cancer chemotherapy. The efficacy, dosage and administration, and other parameters of tasurgratinib should be further evaluated.

PMDA has concluded that tasurgratinib may be approved if it is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

July 17, 2024

Product Submitted for Approval

Brand Name	Tasfygo Tablets 35 mg
Non-proprietary Name	Tasurgratinib Succinate
Applicant	Eisai Co., Ltd.
Date of Application	December 18, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by the Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of the review presented in Section "7.R.2 Efficacy" of the Review Report (1), PMDA has concluded that tasurgratinib has been demonstrated to have a certain level of efficacy in patients with unresectable cholangiocarcinoma with *FGFR2* gene fusion who have received prior chemotherapy in view of the results of the global phase II study (Study 201) and the oncobiological meaning of *FGFR2* gene fusions [see Section 7.R.2.1]. Study 201 was conducted in patients with unresectable cholangiocarcinoma (intrahepatic or hilar cholangiocarcinoma) with *FGFR2* gene fusion who had received prior chemotherapy, and the response rate [90% CI] as assessed by IIR based on RECIST ver.1.1, the primary endpoint of the study, was 30.2% [20.7%, 41.0%] (19 of 63 subjects).

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion.

1.2 Safety

As a result of the review presented in Section "7.R.3 Safety" of the Review Report (1), PMDA has concluded that adverse events requiring special attention during treatment with tasurgratinib are hyperphosphatemia, retinal detachment, eye disorders (except for retinal detachment), nail disorders, and palmar-plantar erythrodysesthesia syndrome.

PMDA has also concluded that although attention should be paid to the occurrence of the above adverse events during treatment with tasurgratinib, tasurgratinib is tolerable as long as physicians with adequate knowledge and experience in cancer chemotherapy take appropriate measures, such as monitoring and management of adverse events, and interruption and dose reduction of tasurgratinib.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusions.

1.3 Clinical positioning and indication

As a result of the review presented in Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that the indication of tasurgratinib should be "unresectable biliary tract cancer with *FGFR2* gene fusion that has progressed after cancer chemotherapy," with the following precautionary statements provided in the "Precautions Concerning Indication" section.

Precautions Concerning Indication

- The efficacy and safety of tasurgratinib as the first-line therapy have not been established.
- The efficacy and safety of tasurgratinib have not been established for adjuvant chemotherapy.
- Eligible patients should be identified by physicians with a full understanding of the information on patients enrolled in clinical studies (e.g., location of the primary lesion) presented in the "Clinical Studies" section and of the efficacy and safety of tasurgratinib.
- Tasurgratinib can be used in patients with *FGFR2* gene fusions confirmed by adequately experienced pathologists or by testing at laboratories with extensive expertise. The testing should be performed using approved *in vitro* diagnostics or medical devices.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion.

PMDA thus instructed the applicant to specify the indication and the "Precautions Concerning Indication" section as presented above, and the applicant accepted it.

1.4 Dosage and administration

As a result of the review presented in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA has concluded that the dosage and administration of tasurgratinib should be "The usual adult dosage is 140 mg of tasurgratinib administered orally once daily in the fasted state. The dose may be reduced according to the patient's condition," with the following precautionary statements provided in the "Precautions Concerning Dosage and Administration" section:

Precautions Concerning Dosage and Administration

- The efficacy and safety of tasurgratinib have not been established for its use in combination with other antineoplastic agents.
- It has been reported that the C_{max} and AUC of tasurgratinib decreased following administration of tasurgratinib with food. To prevent the effect of food, administration of tasurgratinib should be avoided

within 1 hour before and 2 hours after a meal.

- If any adverse reaction to tasurgratinib occurs, tasurgratinib should be interrupted, reduced in dose, or discontinued in accordance with the following criteria:

Guide for dose reduction

Dose reduction level	Dose
Usual dose	140 mg
1-level reduced dose	105 mg
2-level reduced dose	70 mg
3-level reduced dose	35 mg
4-level reduced dose	Discontinuation

Criteria for interruption, dose reduction, and discontinuation in response to adverse drug reactions

Adverse drug reaction	Severity*	Action
Hyperphosphatemia	Serum phosphate levels ≥5.5 mg/dL and ≤7.0 mg/dL	Initiate dietary therapy and/or phosphate-lowering therapy.
	Serum phosphate levels ≥7.1 mg/dL and ≤9.0 mg/dL	Initiate dietary therapy and/or phosphate-lowering therapy. If serum phosphate levels are ≥7.1 mg/dL for 2 weeks, interrupt tasurgratinib until the level returns to ≤7.0 mg/dL. Thereafter, to resume tasurgratinib, reduce the dose to the next lower level.
	Serum phosphate levels ≥9.1 mg/dL	Initiate dietary therapy and/or phosphate-lowering therapy. Interrupt tasurgratinib until the serum phosphate level returns to ≤7.0 mg/dL. To resume tasurgratinib, reduce the dose to the next lower level.
Corneal disorder and retinal disorder	Intolerable Grade 2, or Grade 3	Interrupt tasurgratinib until the event resolves to baseline or Grade ≤1. To resume tasurgratinib, reduce the dose to the next lower level.
	Grade 4	Discontinue tasurgratinib.
Blood disorders	Grade 3	Interrupt tasurgratinib until the event resolves to Grade ≤2. Resume tasurgratinib at the same dose level as that before the interruption.
	Grade 4	Interrupt tasurgratinib until the event resolves to Grade ≤2. To resume tasurgratinib, reduce the dose to the next lower level.
Other adverse drug reactions	Intolerable Grade 2	Interrupt tasurgratinib until the event resolves to baseline or Grade ≤1. To resume tasurgratinib, reduce the dose to the next lower level. Initial dose reduction (from 140 mg to 105 mg) does not require treatment interruption.
	Grade 3	Interrupt tasurgratinib until the event resolves to baseline or Grade ≤1. To resume tasurgratinib, reduce the dose to the next lower level.
	Grade 4 (in cases where non-life-threatening laboratory abnormalities occur, take the same action as that for Grade 3)	Discontinue tasurgratinib.

*: Graded according to NCI-CTCAE ver.4.03.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusion.

PMDA thus instructed the applicant to specify the dosage and administration and the "Precautions Concerning Dosage and Administration" section as presented above, and the applicant accepted it.

1.5 Risk management plan (draft)

The applicant plans to conduct a post-marketing surveillance in all patients treated with tasurgratinib to investigate the safety, and other parameters of tasurgratinib during post-marketing clinical use. The safety specification is defined as hyperphosphatemia, retinal disorder, and eye disorders (except for retinal disorder). The planned sample size is 62 patients, and the observation period is 1 year.

As a result of the review presented in Section "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA has concluded that a post-marketing surveillance should be conducted to collect information on the safety of tasurgratinib during post-marketing clinical use because post-marketing experience and information on the safety of tasurgratinib are not available in or outside of Japan. However, the need to conduct a post-marketing all-case surveillance is low in view of the following points:

- For FGFR inhibitors approved in Japan, a certain amount of safety information is available from the past experience in and outside of Japan, and there are no clear differences between these FGFR inhibitors and tasurgratinib.
- Although information on the safety of tasurgratinib in Japanese patients is limited, no concerns have been identified regarding differences in the safety of tasurgratinib between Japanese and non-Japanese patients.

PMDA has further concluded on the surveillance plan as follows:

- The safety specification of the surveillance should be defined as hyperphosphatemia, retinal detachment, eye disorders (except for retinal detachment), nail disorders, and palmar-plantar erythrodysesthesia syndrome. Information on the safety of tasurgratinib in patients with hepatic impairment should also be collected.
- The planned sample size and observation period of the surveillance should be reconsidered based on the details of the events defined as the safety specification of the surveillance, namely, their incidences in clinical studies.

At the Expert Discussion, the expert advisors supported the above PMDA's conclusions.

On the basis of the above discussion, PMDA instructed the applicant to reconsider the surveillance plan.
The applicant's response:

- The safety specification of the surveillance will be defined as hyperphosphatemia, retinal detachment, eye disorders (except for retinal detachment), nail disorders, and palmar-plantar erythrodysesthesia syndrome. The surveillance will also collect information on the safety of tasurgratinib in patients with hepatic impairment.
- The planned sample size and observation period of the surveillance will be 60 patients and 1 year, respectively, based on the incidences of the safety specification events in clinical studies.

PMDA accepted the applicant's response.

On the basis of the above discussion, PMDA has concluded that the risk management plan (draft) for tasurgratinib should include the safety specification presented in Table 52, and that the applicant should conduct the additional pharmacovigilance activities and additional risk minimization activities presented in Table 53 and Table 54.

Table 52. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hyperphosphatemia • Retinal detachment	• Eye disorders (except for retinal detachment) • Nail disorders • Palmar-plantar erythrodysesthesia syndrome • Use in patients with hepatic impairment • Embryo-fetal toxicity	None
Efficacy specification		
None		

Table 53. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey in patients with unresectable biliary tract cancer with *FGFR2* gene fusion that has progressed after cancer chemotherapy	None	• Provision of information collected through early post-marketing phase vigilance • Preparation and provision of materials for healthcare professionals • Preparation and provision of materials for patients

Table 54. Outline of use-results survey (draft)

Objective	To investigate the safety, etc. of tasurgratinib in routine clinical practice.
Survey method	Central registry
Population	Patients with unresectable biliary tract cancer with *FGFR2* gene fusion that has progressed after cancer chemotherapy, who were treated with tasurgratinib
Observation period	1 year
Planned sample size	60 patients
Main survey items	Safety specification: Hyperphosphatemia, retinal detachment, eye disorders (except for retinal detachment), nail disorders, and palmar-plantar erythrodysesthesia syndrome Other main survey items: Patient characteristics (e.g., age, sex, location of the primary lesion, prior treatment, medical history or complications, and severity of hepatic impairment), status of tasurgratinib treatment, adverse events, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition, provided that tasurgratinib is administered under the supervision of a physician who has adequate knowledge and experience of cancer chemotherapy at a medical institution that is fully capable of managing emergencies, to ensure proper use of the product. The product has been designated as an orphan drug, and the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Unresectable biliary tract cancer with *FGFR2* gene fusion that has progressed after cancer chemotherapy

Dosage and Administration

The usual adult dosage is 140 mg of tasurgratinib administered orally once daily in the fasted state. The dose may be reduced according to the patient’s condition.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Warnings

The product should be administered only to patients assessed as eligible to receive treatment with the product under the supervision of a physician who has adequate knowledge and experience of cancer chemotherapy at a medical institution that is fully capable of managing emergencies. Prior to treatment, the patient or his/her family member should be fully informed of the benefits (efficacy) and risks of the treatment, and consent should be obtained.

Contraindication

Patients with a history of hypersensitivity to any of the excipients of the product

Precautions Concerning Indication

1. The efficacy and safety of tasurgratinib as first-line therapy have not been established.
2. The efficacy and safety of tasurgratinib have not been established for adjuvant chemotherapy.
3. Eligible patients should be identified by physicians with a full understanding of the information on patients enrolled in clinical studies (e.g., location of the primary lesion) presented in the "Clinical Studies" section and of the efficacy and safety of tasurgratinib.
4. Tasurgratinib can be used in patients with *FGFR2* gene fusions confirmed by adequately experienced pathologists or by testing at laboratories with extensive expertise. The testing should be performed using approved *in vitro* diagnostics or medical devices.

Precautions Concerning Dosage and Administration

1 The efficacy and safety of tasurgratinib have not been established for its use in combination with other antineoplastic agents.

2 It has been reported that the C_{max} and AUC of tasurgratinib decreased following administration with food. To prevent the effect of food, administration of tasurgratinib should be avoided within 1 hour before and 2 hours after a meal.

3 If any adverse reaction to tasurgratinib occurs, tasurgratinib should be interrupted, reduced in dose, or discontinued in accordance with the following criteria:

Guide for dose reduction

Dose reduction level	Dose
Usual dose	140 mg
1-level reduced dose	105 mg
2-level reduced dose	70 mg
3-level reduced dose	35 mg
4-level reduced dose	Discontinuation

Criteria for interruption, dose reduction, and discontinuation in response to adverse drug reactions

Adverse drug reaction	Severity*	Action
Hyperphosphatemia	Serum phosphate levels ≥5.5 mg/dL and ≤7.0 mg/dL	Initiate dietary therapy and/or phosphate-lowering therapy.
	Serum phosphate levels ≥7.1 mg/dL and ≤9.0 mg/dL	Initiate dietary therapy and/or phosphate-lowering therapy. If serum phosphate levels are ≥7.1 mg/dL for 2 weeks, interrupt tasurgratinib until the level returns to ≤7.0 mg/dL. Thereafter, to resume tasurgratinib, reduce the dose to the next lower level.
	Serum phosphate levels ≥9.1 mg/dL	Initiate dietary therapy and/or phosphate-lowering therapy. Interrupt tasurgratinib until the serum phosphate level returns to ≤7.0 mg/dL. To resume tasurgratinib, reduce the dose to the next lower level.
Corneal disorder and retinal disorder	Intolerable Grade 2, or Grade 3	Interrupt tasurgratinib until the event resolves to baseline or Grade ≤1. To resume tasurgratinib, reduce the dose to the next lower level.
	Grade 4	Discontinue tasurgratinib.
Blood disorders	Grade 3	Interrupt tasurgratinib until the event resolves to Grade ≤2. Resume tasurgratinib at the same dose level as that before the interruption.
	Grade 4	Interrupt tasurgratinib until the event resolves to Grade ≤2. To resume tasurgratinib, reduce the dose to the next lower level.
Other adverse drug reactions	Intolerable Grade 2	Interrupt tasurgratinib until the event resolves to baseline or Grade ≤1. To resume tasurgratinib, reduce the dose to the next lower level. Initial dose reduction (from 140 mg to 105 mg) does not require treatment interruption.
	Grade 3	Interrupt tasurgratinib until the event resolves to baseline or Grade ≤1. To resume tasurgratinib, reduce the dose to the next lower level.
	Grade 4 (in case where non-life-threatening laboratory abnormalities occur, take the same action as that for Grade 3)	Discontinue tasurgratinib.

*: Graded according to NCI-CTCAE ver.4.03.

Appendix

List of Abbreviations

A/G ratio	albumin-globulin ratio
AKT	Protein kinase B
AHCYL1	Adenosylhomocysteinase like 1
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BCRP	breast cancer resistance protein
BICC1	BicC family RNA binding protein 1
^{14}C-labeled	^{14}C-labeled tasurgratinib
CHO cell	Chinese hamster ovary cell
CI	confidence interval
CL/F	apparent clearance
CMV	cytomegalovirus
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CrCL	creatinine clearance
CYP	cytochrome P450
DDR	Discoidin domain receptor
DLT	dose-limiting toxicity
DMSO	dimethyl sulfoxide
ECOG	Eastern Cooperative Oncology Group
efflux ratio	ratio of apparent permeability coefficient in the secretory direction to that in the absorptive direction
eGFR	estimated glomerular filtration rate
ERK	extracellular signal-regulated kinase
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FISH	fluorescence *in situ* hybridization
GC	gas chromatography
GGT	γ-glutamyl transferase
HCl	hydrochloric acid
hERG	human *ether-a-go-go* related gene
HPLC	high performance liquid chromatography
5-HT	5-hydroxytryptamine
HUVEC	human umbilical vein endothelial cell
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E guideline	“Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
CH Q3A guideline	“Impurities in New Drug Substances” (PFSB/ELD Notification No. 1216001 dated December 16, 2002)
CH Q3B guideline	“Impurities in New Drug Products” (PFSB/ELD Notification No. 0624001 dated June 24, 2003)
IIR	independent imaging review
IR	infrared absorption spectrum
KCTD1	potassium channel tetramerization domain containing 1

LC-MS/MS	liquid chromatography-tandem mass spectrometry
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MPE	mean photo effect
mRNA	messenger ribonucleic acid
MS	mass spectrum
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NE	not evaluable
[redacted]	[redacted]
NMR	nuclear magnetic resonance spectrum
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
PD	progressive disease
PFS	progression free survival
P-gp	P-glycoprotein
PIF	photo-irritancy factor
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetics
PPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
PTP	press through packaging
QD	quaque die
(Q) SAR	(quantitative) structure-activity relationship
QT	QT interval
QTc	QT interval corrected
ΔQTcF	change in Fridericia-corrected QT from baseline
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
RH	relative humidity
RP2D	recommended Phase 2 dose
RTRT	real time release testing
S-1	combination drug of tegafur, gimeracil, and oteracil potassium
SD	stable disease
SMQ	standardised MedDRA queries
SOC	system organ class
TACC3	transforming acidic coiled-coil containing protein 3
TXLNA	taxilin alpha
UV	ultraviolet
UV-VIS	ultraviolet-visible spectrum
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
V_2/F	apparent central volume of distribution
V_3/F	apparent peripheral volume of distribution
PMDA	Pharmaceuticals and Medical Devices Agency
gemcitabine	gemcitabine hydrochloride
Study 002	Study E7090-E044-002
Study 003	Study E7090-J081-003

Study 101	Study E7090-J081-101
Study 201	Study E7090-J000-201
application	application for marketing approval
tasurgratinib	Tasurgratinib Succinate
rabeprazole	rabeprazole sodium